B9

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2002 (10.05.2002)

PCT

(10) International Publication Number
WO 02/36597 A1

(51) International Patent Classification[7]: C07D 491/04, 471/04, 209/80, 209/86, A61K 31/404, A61P 35/00

(21) International Application Number: PCT/IT01/00526

(22) International Filing Date: 16 October 2001 (16.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
RM2000A000570
3 November 2000 (03.11.2000) IT

(71) Applicant *(for all designated States except US)*: **SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.** [IT/IT]; Viale Shakespeare, 47, I-00144 Rome (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GIANNINI, Giuseppe** [IT/IT]; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina, km 30, 400, I-00040 Pomezia (IT). **MARZI, Mauro** [IT/IT]; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina, km 30, 400, I-00040 Pomezia (IT). **TINTI, Maria, Ornella** [IT/IT]; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina, km 30, 400, I-00040 Pomezia (IT). **PISANO, Claudio** [IT/IT]; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina, km 30, 400, I-00040 Pomezia (IT).

(74) Agent: **SPADARO, Marco**; Cavattoni - Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *of inventorship (Rule 4.17(iv)) for US only*

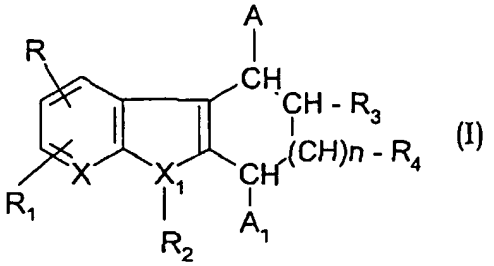
Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRICYCLIC DERIVATIVES OF INDOLE WITH ANTIANGIOGENIC ACTIVITY



(I)

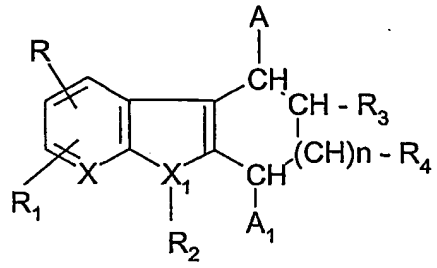
(57) Abstract: Compounds of formula (I), in which the groups are as definite in the description, useful as medicaments endowed with cytotoxic and antiangiogenic activity, are described.

WO 02/36597 A1

TRICYCLIC DERIVATIVES OF INDOLE WITH ANTIANGIOGENIC ACTIVITY

The invention described herein relates to compounds having tricyclic structure of the type tetrahydrociclopent[b]indole (1), tetrahydrocarbazole (2), and esahydrocycloept[b]indole (3), a processes for their preparations, and pharmaceutical composition containing the same for treating tumor and diseases associated with abnormal angiogenesis.

Said compounds have the following general formula (I):



(I)

wherein:

X = CH, N

X_1 = O, S, N, CH

R and R_1, which may be the same or different, are selected from the group consisting of: -H, OH, OR_5 in which R_5 may be C_1-C_4 alkyl or benzyl, when two groups OR_5 are vicinal R_5 is methylen; or R and R_1 may be independently nitro; amino possibly mono- or di-substituted with C_1-C_4 alkyl; carboxy; alkoxy (C_1-C_4) carbonyl;

R and R_1 taken together may form an aliphatic or aromatic cyclic group having 5 or 6 atoms;

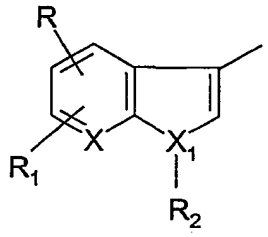
when X_1 = N, CH, then

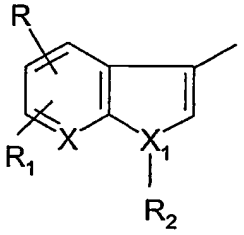
R_2 is selected from the group consisting of –H, phenyl, benzyl, linear or branched C_1-C_6 alkyl;

n = is an integer ranging from 0 and 4;

R_3, which may be the same as or different from R_4, may be: -H, - OH, - OR_6, wherein

R_6 is linear or branched C_1-C_4 alkyl, or when R_3 = R_4 = OR_6 vicinal, R_6 is isopropyliden

A =  with A_1 = H

A_1 =  with A = H, R_7

R_7 = C_1-C_4 linear or branched alkyl possibly substituted with one or two groups OH, OR_6, in case of 2 groups OR_6 vicinal, R_6 is isopropyliden; or R_7 is formyl (CHO), oxime (CH=NOH).

The invention includes all the possible isomers, stereoisomers and their mixtures, metabolites and their metabolic precursors or bio-precursors (so called pro-drug) of the general formula.

The use of antineoplastic drugs in human therapy causes a substantial number of toxic or side effects which consequently lead to a reduction of the amount of drug to be administered, and in some cases to discontinuation of the therapy. A reduction of the amount of drug to be administered or discontinuation of the therapy cause an increase in primary tumour growth and/or the occurrence of tumour metastases.

The growth of a primary tumour is favoured by good vascularisation (by angiogenesis) of the tumour tissue. An adequate supply of oxygen and nutrients promotes rapid growth of the tumour itself. It has been demonstrated that the extent of angiogenesis can be an extremely negative factor in the prognosis of neoplasms.

Angiogenesis in the adult is normally quiescent, but it represents a normal function, for example in the healing of wounds, or in the reconstruction of the endometrium during the female reproductive cycle.

The angiogenic response is physiologically stimulated when the vascular functions are reduced and tissue perfusion is inadequate.

More generally, it can be claimed that, in physiological conditions, angiogenesis constitutes a positive feedback in response to inadequate perfusion, or to a reduced supply of oxygen and nutrients, such as occurs, for instance, in the case of occlusion of an artery, in situations of tissue mass growth (for example, the neovascularisation that accompanies the formation of muscle

tissue); and in the case of an increased work load in association with an increased oxygen and nutrient requirement.

In the course of local ischaemia, due to partial or complete occlusion of an artery, the development of collateral vessels is necessary in order to maintain perfusion.

As above mentioned, it has been demonstrated that the extent of angiogenesis can be an extremely negative factor in the prognosis of neoplasms (van Hinsbergh VW, Collen A, Koolwijk P; Ann. Oncol., 10 Suppl., 4:60-3, 1999; Buolamwini JK; Curr. Opin. Chem. Biol., 3(4):500-9, 1999 Aug.).

It is also known, in the neoplastic field, that a fundamental stage in the biology of the tumour cell is the acquisition of metastasising capability.

The tumour cells that metastasise are able to lose adherence to the surrounding structures, invade blood and lymphatic vessels and colonise other tissues at a distance where they can continue to reproduce themselves.

Metastasising is also a critical event in the clinical history of the disease, being the main cause of death due to cancer. It is closed associated with and facilitated by the presence of vascular tissue in the tumour site or adjacent areas.

The migration of tumour cells across the surrounding structures enables the cells to reach the intratumoural blood vessels, whether pre-existing or formed by neo-angiogenesis, and

thus reach the bloodstream (Ray JM., Stetler-Stevenson WG; Eur. Respir. J., 7(11):2062-72, 1994; Stetler-Stevenson WG, Liotta LA, Kleiner DE Jr.; FASEB J., 7(15):1434-41, 1993 Dec.).

The presence of communication between lymphatic and blood vessels in the vascular region of the tumour enables the neoplastic cells to move in both vascular systems.

Recent studies have shown a direct relationship between angiogenesis and arthritic disease (Koch AE; Arthritis and Rheumatism 41:951-962, 1998). In particular, it has been demonstrated that neo-vascularisation of the articular cartilages plays a crucial role in pannus formation and in progression of arthritis. A normal cartilage does not possess blood vessels, while the synovial fluid of arthritic patients contains an angiogenesis-stimulating factor produced by endothelial cells (EASF).

The presence of this factor is associated with vascularisation and degradation of the cartilage.

Other diseases are also related to abnormal angiogenesis.

It has been found that, in diabetic retinopathy [Histol. Histopathol. 1999 Oct; 14(4):1287-94], psoriasis [Br J.Dermatol. 1999 Dec; 141(6):1054-60], chronic inflammation and arteriosclerosis [Planta Med. 1998 Dec; 64(8):686-95], neovascularisation of the affected tissues is a facilitating factor.

Over the past thirty years compounds with a cycloalkanoindole structure have been synthesised and studied with a view to exploiting their possible therapeutic potential.

The basic requisite of these compounds - the substituted indole in position 3 - is a feature shared by natural products such as melatonin or tryptophan.

In the '70s, cycloalkanoindole compounds were studied for their antiinflammatory properties (J.Med.Chem. 1976, 19(6):787-92) or for their antidepressant properties (J.Med.Chem. 1976, 19(6):792-7).

These studies were then followed by others (on a number of aminotetrahydrocarbazols) to assess their effects on the CNS (J.Med.Chem. 1977, 20(4):487-92) in that they possessed a tryptamine-like structure.

In the '80s, a number of derivatives with a tetrahydrocarbazol structure were found to possess antibacterial properties: in culture they inhibit the growth of *Trypanosoma cruzi* (Rev. Argent. Microbiol. 1987, 19(3):121-4).

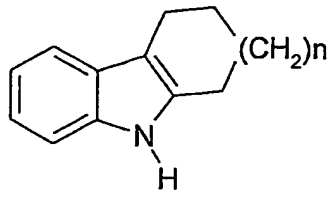
In the '90s, compounds with a cycloalkanoindole structure were studied as potential analgesics (Xenobiotica 1989, 19(9):991-1002), with effects on the serotonin receptors (J.Med.Chem. 1993, 36(13): 1918-9) and on the melatonin receptors (Eur. J.Pharmacol. 1995, 287(3):239-43).

In the past few years, tetrahydrocarbazol derivatives have been studied for their antiproliferative properties (Farmaco 1998, 53(6):431-7); in particular, the N-pyridinium derivative may act with a mechanism involving inhibition of topoisomerase II.

US 5,017,593 describes derivatives of cyclohept[b]indole alkanoic acid as leukotriene antagonists.

EP 0496237 describes N-imidazolyl derivatives of tetrahydrocarbazol and cyclohept[b]indoles as thromboxane antagonists (TXA-2), useful in the treatment of cardiovascular disorders (myocardial infarction and angina), cerebrovascular disease (stroke, transient ischaemic attacks, migraine), peripheral vascular disease (microangiopathy), kidney disease (glomerular sclerosis, lupus nephritis, diabetic nephropathy), respiratory disease (bronchoconstriction and asthma) and atherosclerosis.

J. Med. Chem. 1998, 41, 451-67 describes compounds with tetrahydrocyclopent[b]indole (1), tetrahydrocarbazol (2), and hexahydrocyclohept[b]indole (3) structures used for studies on melatonin receptors having formula:

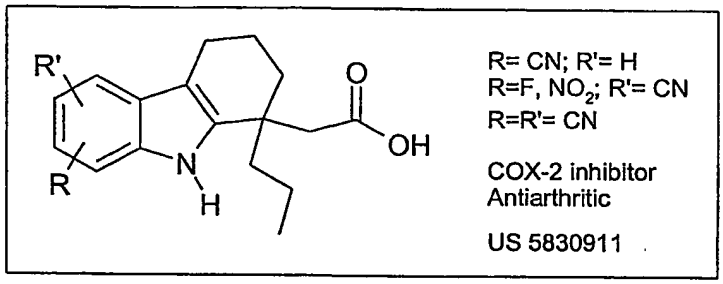


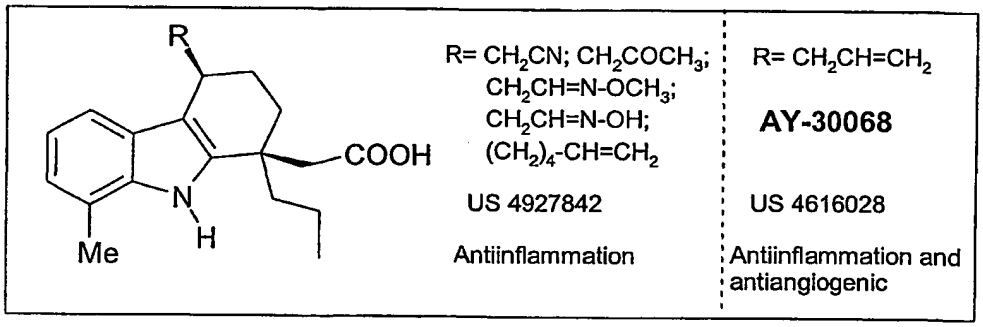
(1) n = 0 **tetrahydrocyclopent[b]indole**

(2) n = 1 **tetrahydrocarbazole**

(3) n = 2 **hexahydrocycloept[b]indole**

US 5,830,911; US 4,927,842; US 4,616028 describe tetrahydrocarbazol compounds, with antiinflammatory activity having formula:





The compounds described in the above cited publications are different from those claimed in the present invention.

Despite the progress made in recent years, the pharmacological research concerned with discovering new drugs for the treatment of tumor diseases and diseases characterised by abnormal angiogenesis is still considered by many experts in medicine as one of the most promising field.

In fact, to date there is still a strongly perceived need for new compounds capable of blocking or interfering with the tumour

diseases and diseases caused by abnormal angiogenesis. As mentioned above, these diseases include tumours, tumours metastasis, arthritic diseases, diabetic retinopathy, psoriasis, chronic inflammation and arteriosclerosis.

It has now been found that the formula (I) compounds, characterised by the presence of two aromatic bases (indole or one of its derivatives), where the first is condensed to a saturated cycle in position 2-3, of the tetrahydrocarbazol type, and the second aromatic base, bound in position 3, is present as a substituent in the benzyl position of the saturated ring, unexpectedly possess antitumor and antiangiogenic properties.

Compounds with general formula (I) are therefore the object of the invention described herein.

A further object of the invention described herein are compounds with general formula (I) and their use in the medical field.

A further object of the invention described herein are compounds with general formula (I) and a process for their preparation.

A further object of the invention described herein is a pharmaceutical composition containing as active ingredient a formula (I) compound and at least a pharmaceutically acceptable excipient and/or diluent.

A further object of the invention described herein is a pharmaceutical composition containing as active ingredient a formula (I) compound, for the treatment of a tumour pathology, in which the tumour is selected from the group consisting of sarcoma, carcinoma, carcinoid, bone tumour, neuroendocrine tumour, lymphoid leukaemia, acute promyelocytic leukaemia, myeloid leulaemia, monocytic leukaemia, megakaryoblastic leukaemia and Hodgkin's disease.

A further object of the invention described herein is the use of compounds of formula (I) for the preparation of a medicament with antiangiogenic activity.

A further object of the invention described herein is the use of compounds of formula (I) for preventing the onset of tumour metastases.

A further object of the invention described herein is the use of compounds of formula (I) for the treatment of arthritic disease.

A further object of the invention described herein is the use of compounds of formula (I) for the treatment of diabetic retinopathy.

A further object of the invention described herein is the use of compounds of formula (I) for the treatment of psoriasis.

A further object of the invention described herein is the use of compounds of formula (I) for the treatment of chronic inflammatory diseases.

A further object of the invention described herein is the use of compounds of formula (I) for the treatment of arteriosclerosis.

As mentioned above, the growth of a primary tumour is facilitated by good vascularisation of the tumour tissue, and the extent of the neoangiogenesis may be a highly adverse factor in the prognosis of neoplasms. An adequate supply of oxygen and nutrients in the tumour site, in fact, facilitates rapid growth of the tumour itself.

It is well known that the therapeutic measures available to physicians for the treatment of tumours are still unable to prevent many patients from dying of these diseases. It is also well known that most oncological patients are treated not with a single anticancer drug but with a combination of several anticancer agents. The need to administer anticancer drugs in combination stems from the fact that by acting at different metabolic levels in some cases they favour complete remission of the tumour, while in others they lengthen the patient's life and/or improve the quality of life of the patients treated.

To date there is still a strongly perceived need for new compounds to be used in combination with known compounds in the fight against cancer.

The compound according to the invention described herein can be used in combination with one or more anticancer drugs.

A further object of the invention described herein is the combination of compounds of formula (I) with one or more known anticancer drugs.

A further object of the invention described herein is a pharmaceutical composition containing the combination of compounds of formula (I) with one or more known anticancer drugs, and one or more excipients or vehicles pharmacologically acceptable.

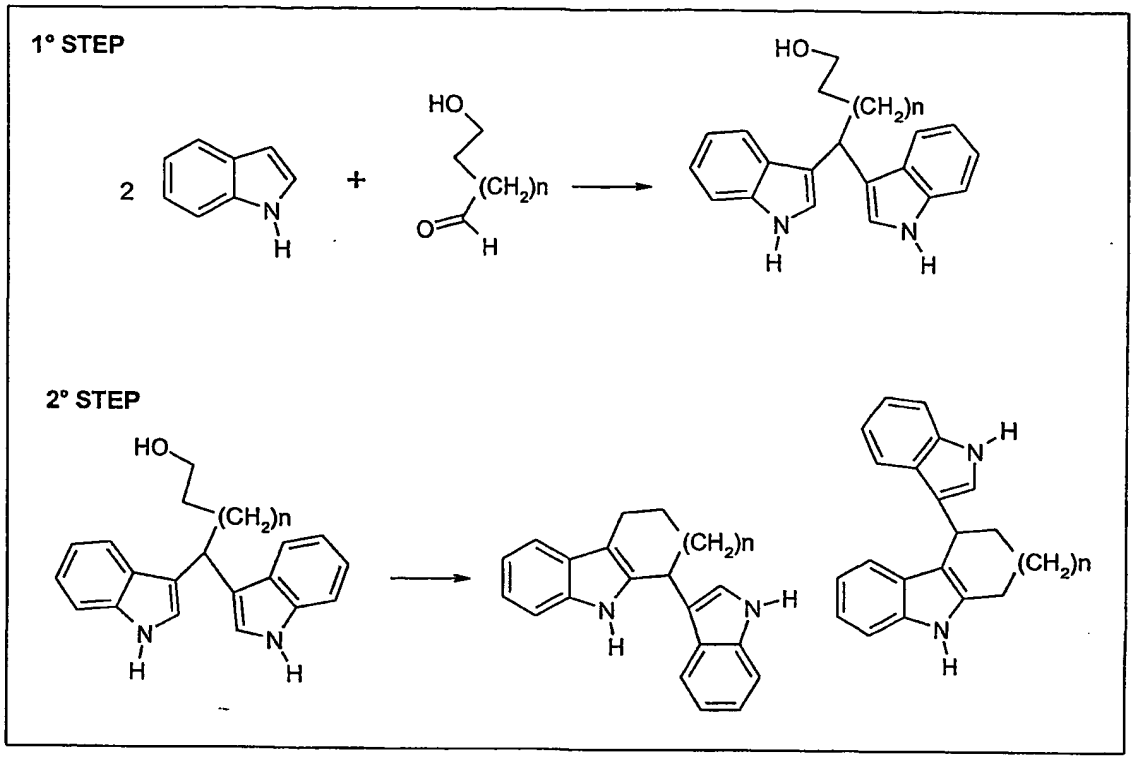
A further object of the invention described herein is a pharmaceutical composition containing as active ingredient a formula (I) compound, in combination with one or more known antitumour compounds, in which the antitumour compound is selected from the group consisting of alkylating agents, topoisomerase inhibitors, antitubulin agents, intercalating compounds, anti-metabolites, natural products such as vinca alkaloids, epipodophyllotoxins, antibiotics, enzymes, taxans, and cyto-differentiating compounds.

A further object of the invention described herein is the use of the combination of compounds of formula (I) and the anticancer compound to prepare a medicament for the treatment of tumour, characterised in that the compound of formula (I) is present as a coadjuvant of the anticancer compound.

The following examples illustrate the invention

The synthesis of cyclised products consists of two stages: the first stage consists in the condensation, in the geminal position, of a

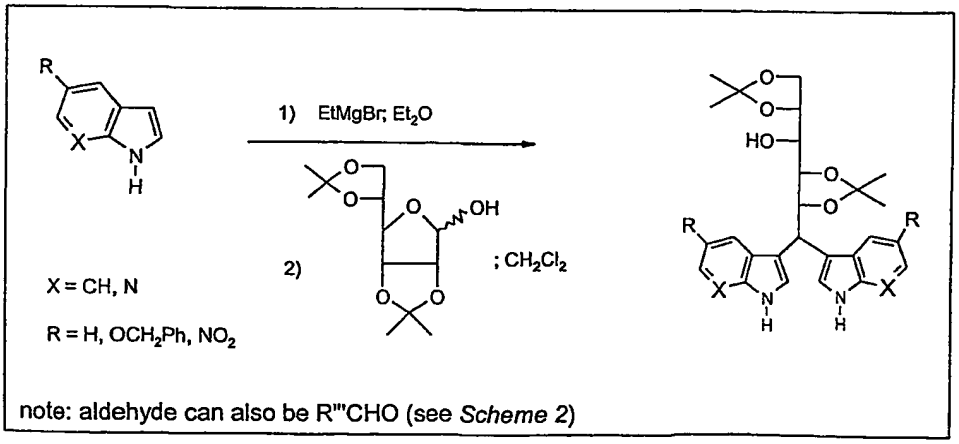
hydroxyaldehyde with 2 aromatic bases; the second stage consists in a cyclisation reaction with DAST (diethyl amino-sulphur trifluoride). This synthetic sequence, albeit with exceptions, may represent the synthesis process adopted in the preparation of all the derivatives described herein. For the sake of simplicity of description, the case of formula (I) compounds where dove X is CH, X_1 is NH, and R_3 and R_4 are hydrogen is illustrated. It is perfectly clear that the expert in the sector can prepare all the formula (I) compounds using suitable starting materials and adopting suitable reagents, simply by availing himself or herself of his own general knowledge, or with the aid of the standard manuals available.



As the expert in the sector will readily appreciate, the first stage in the synthesis involves the preparation of intermediate products with a bisindole structure.

Their preparation can be done using various different methods.

PROCEDURE A: Synthesis of derivatives with mannofuranose

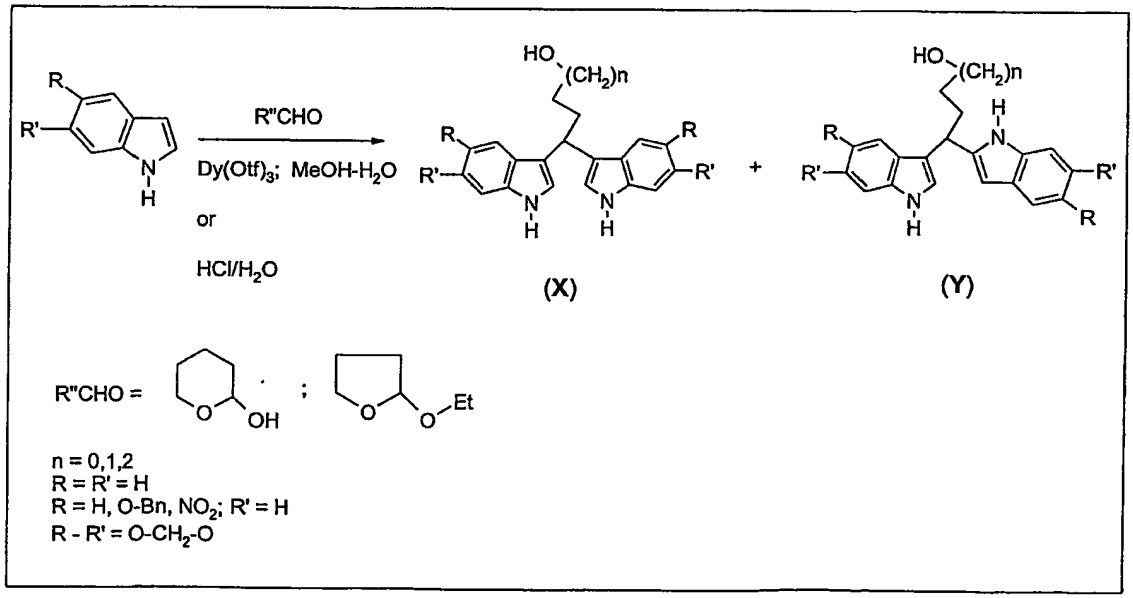


Scheme (1)

Reaction (Tetrahedron Asymmetry, 1997, 8(17), 2905-12): The indole or its derivatives (1mmol) was dissolved in Et_2O anhydrous (50ml). A solution of ethylmagnesiumbromide/ether (3M) (0.33ml; 1mmol) was slowly added. The solution so obtained was left under stirring, in anhydrous conditions, for several minutes: a magnesium white salt derivative was obtained. The ether was evaporated the white residual obtained was dissolved in anhydrous CH_2Cl_2. The solution was left at room temperature/reflux for 12/36h.

Work-up: the solution was quenched by addition of a saturated solution of $NaHCO_3$/10%NH_4Cl. The organic phase was separated and dried on Na_2SO_4 and evaporated. The desired product was purified by flash chromatography (hexane/acetone).

PROCEDURE B: Synthesis of hydroxyaldeide derivatives

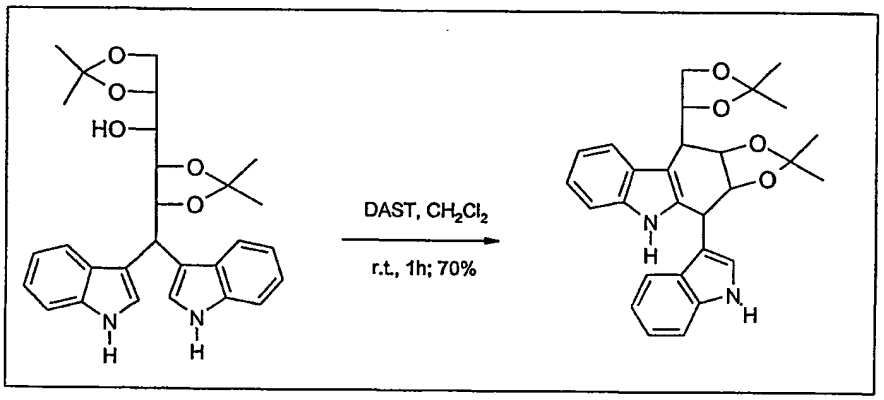


Scheme (2)

Reaction: the indole or its derivative (2mmol) was dissolved with the aldehyde (5-hydroxy-pentanale or 2-etoxytetrahydrofurano) (1mmol), in 15ml of MeOH/ H_2O (2/1). finally Dysprosium triflate was added and the mixture was left to react at room temperature/80°C for 6/36h.

Work-up: The reaction mixture was quenched with 10% $NaHCO_3$, extracted with CH_2Cl_2. The extracted were dried Na_2SO_4, and evaporated. The raw residual was purified by preparative-HPLC and two regioisomers were isolated (X) and (Y).

Procedure C: Reaction of cyclization on mannofuranose derivatives



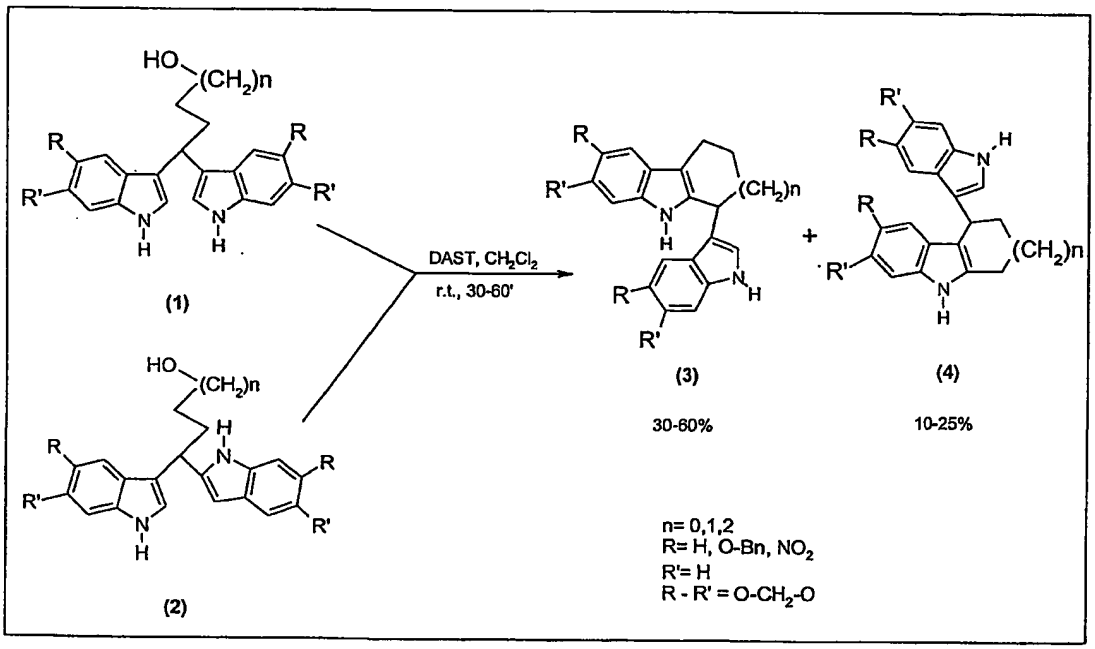
Scheme (3)

Reaction: The bis-indolyl derivative (476mg; 1mmol) was dissolved in CH_2Cl_2 (80ml). At the solution was added, at room temperature, diethylaminosulfur trifluoride (DAST) (400µl; 3mmol). The reaction was rapid.

Work-up: after 60' a solution of10% $NaHCO_3$ was added, and the solution was extracted with CH_2Cl_2. The organic extracted were

dried on Na_2SO_4 and evaporated. The reaction products present in this raw reaction product were isolated by preparative-TLC or better by preparative-HPLC RP-18.

Procedure D: Reaction of cyclization on derivatives with hydroxyaldehyde



Scheme (4)

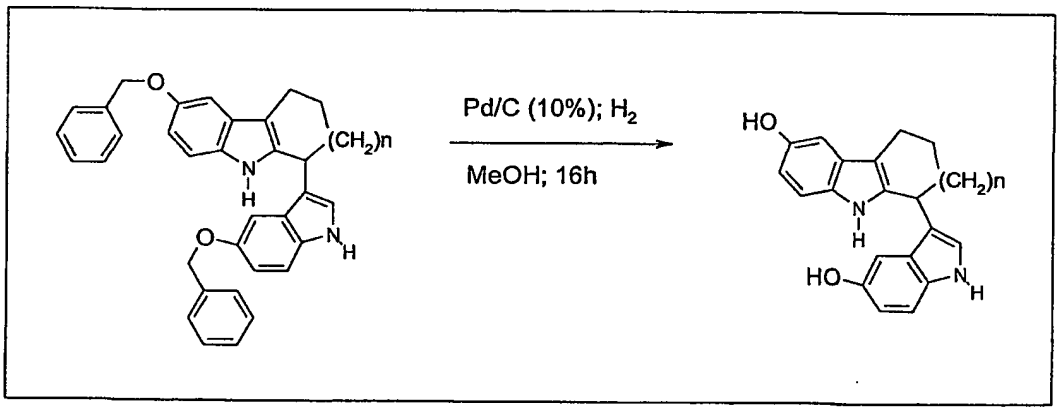
Reaction: the symmetric derivative (1) or asymmetric derivative (2) (1mmol) was dissolved in CH_2Cl_2 (20ml). DAST (200µl; 1,5mmol) was added to the solution, at 0°C – room temperature. The reaction was rapid. After 15'-20' the starting product was almost completely reacted.

Work-up: after 30' a solution of 10% $NaHCO_3$ was added, the solution so obtained was extracted with CH_2Cl_2. The organic

extracted were dried on Na_2SO_4 and evaporated. The reaction products present in this raw reaction product were isolated by preparative-TLC or better by RP-18 prep.-HPLC.

Starting from the symmetric or from the non-symmetric product were formed both, the derivative with the second indole residual toward the lower part (3) with a yield of 30-60% and the derivative with the indole residual toward the high part (4): the latter is present in 10-25% respect to the other.

Procedure E: Debenzylation reaction



Scheme (5)

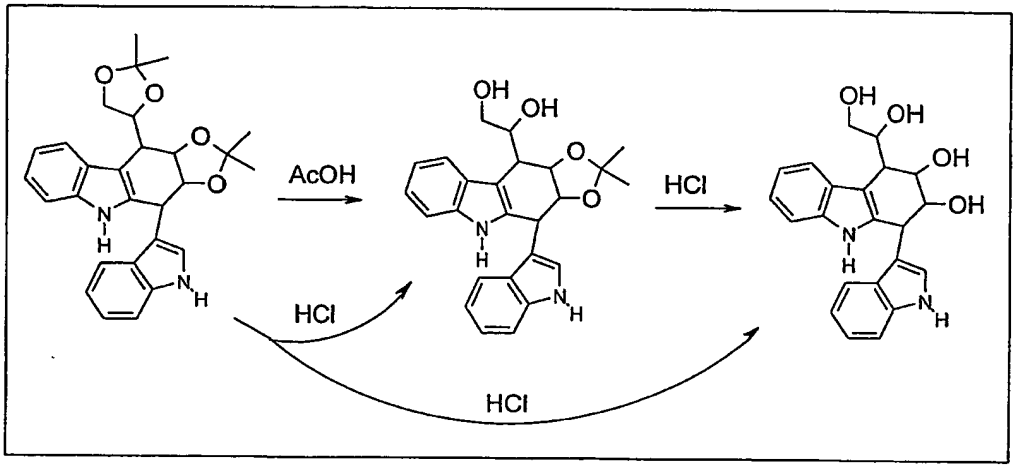
Reaction: the benzylated derivative (1mmol) was dissolved in CH_3OH (50ml)

The catalyst (10%Pd/C; 30mg) was added to the solution, at room temperature.

The solution so obtained was left under hydrogen (60 psi). After 16 h the starting product was completely reacted.

Work-up: The catalyst was filtered of. The organic phase was evaporated. The deprotected product was purified by flash-chromatography. Yield 85%.

Procedure F: Deprotection reaction



Scheme (6)

Reaction: the protect product (1mmol) was dissolved in tetrahydrofuran (THF) (50ml). HCl 1N was added to the solution. The solution so obtained was left for 1h at 20°C - 40°C. So the starting product was completely reacted. The principal deprotect product obtained was the desired product.

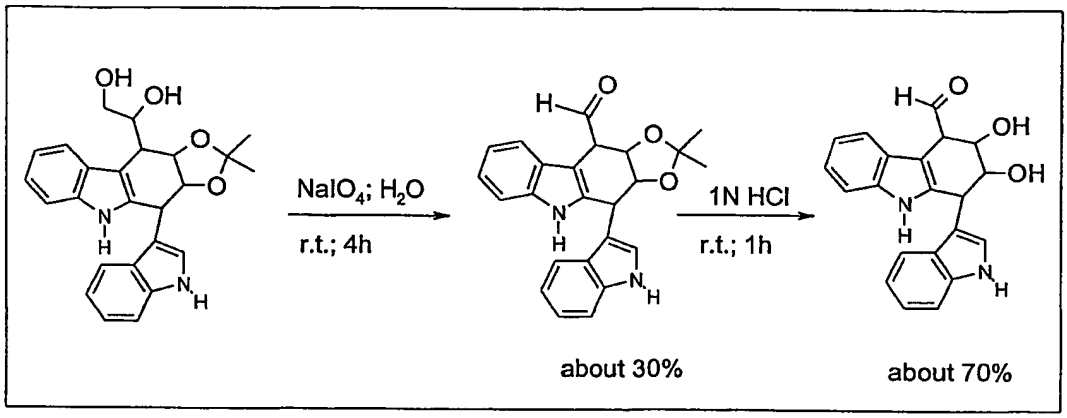
With reference to the deprotected product only in the esocyclic residual, the deprotection can be obtained by acid hydrolysis at low temperature (ex. 1N HC at low temperature, for 30'-60').

Work-up: the obtained product (vedi es. 1)was shacked with a saturated solution of $NaHCO_3$. The THF was evaporated, then the product was extracted with AcOEt. The organic phase was

evaporated end the deprotected product was purified by flash-chromatography.

Yield 85%.

Procedure G: Oxydation reaction.



Scheme (7)

Reaction: The aldehyde (1 mmol) was dissolved in 20 mL of MeOH. To the solution was added NaIO4 (1 mmol) dissolved in 2 mL of H_2O.

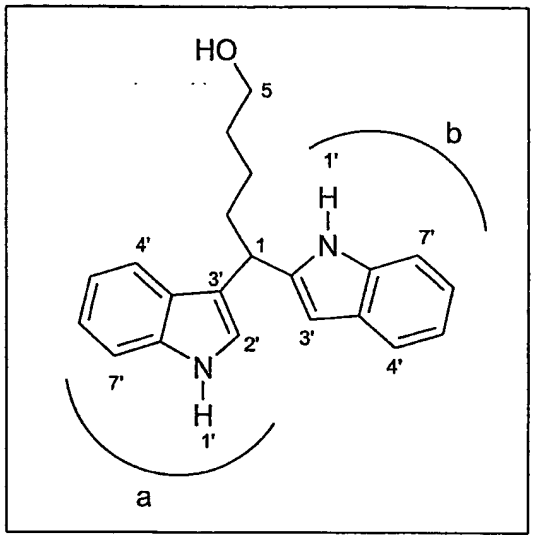
The solution so obtained was left at room temperature for 4h.

Work-up: 1° Step: a $Na_2S_2O_3$ aqueous solution was added. The organic solvent was evaporated and the residual was extracted with AcOEt.

2° Step: the protect intermediate can be deprotected as described in scheme 6.

EXAMPLE 1

ST 1345



(R,S)-5-hydroxy-1,1-(indol-2-yl, indol-3-yl)-pentan

TLC (Exane/Isopropanol=97.5/2.5): 0.5

HPLC RP-18 Waters 250x4.6 (70%H_2O, 30%CH_3CN, Flow 1ml/min): 6.16

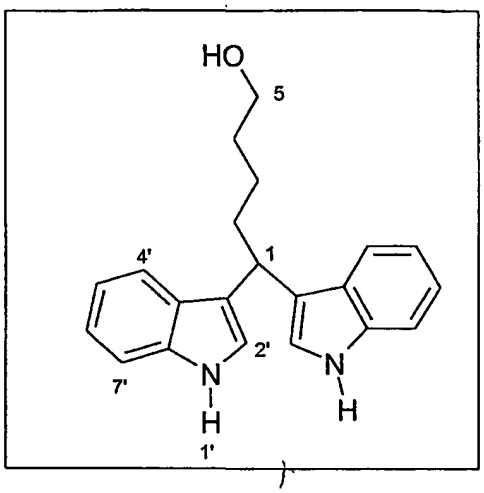
NMR 300MHz (H-1, $CDCl_3$): H_1(4.30 t, 1H) - H_5(3.5 t, 2H) – $H_{2\text{-}4}$(1.4-1.5-2.1 m, 6H) - $H_{1'b}$ – $H_{1'a}$ (7.8-8.0 s, 2H) – $H_{4'b}$(7.5 m, 1H) – $H_{7'a}$(7.4 d, 1H) – $H_{7'b}$(7.22 d, 1H) – H4'a-$_{5'a\text{-}5'b\text{-}6'a\text{-}6'b}$-(6.9-7.2 m, 5H) – $H_{2'a}$(6.96 d, 1H) – $H_{3'b}$(6.4 d, 1H)

Ion Spray (M^-): 317

Elemental analysis: (calculated) C:79.21% H:6.96% N:8.79% (found) C:78.64% H:7.15% N:8.45%

EXAMPLE 2

ST 1346



5-Hydroxy-1,1-di-(indol-3-yl)-pentane

TLC (Exane/iPrOH=97.5/2.5): 0.43

HPLC RP-18 Waters 250x4.6 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 5.36

NMR 300MHz (H-1, $CDCl_3$): H_1(4.7 t, 1H) – H_5(3.8 t, 2H) – H_4(2.3 m, 2H) - H_3(1.7 m, 2H) – H_2(1.8 m, 2H) - $H_{2'}$(7.2 s, 2H) – $H_{5'}$(7.15 t, 2H) - $H_{6'}$(7.4 t, 2H) - $H_{4'}$(7.5 d, 2H) - $H_{7'}$(7.8 d, 2H) – $H_{1'}$(8.15 br.s, 2H)

NMR 300MHz (C-13, $CDCl_3$): C_1(34.2) – C_2(33.0) - C_3(24.6) - C_4(35.7) – C_5(63.2) – $C_{7'}$(111.2) – $C_{6'}$(119.2) - $C_{4'}$(119.8) – $C_{3'}$(120.4) – $C_{5'}$(121.6) – $C_{2'}$(122) – $C_{3'bis}$(127.2) – $C_{7'bis}$(136.7)

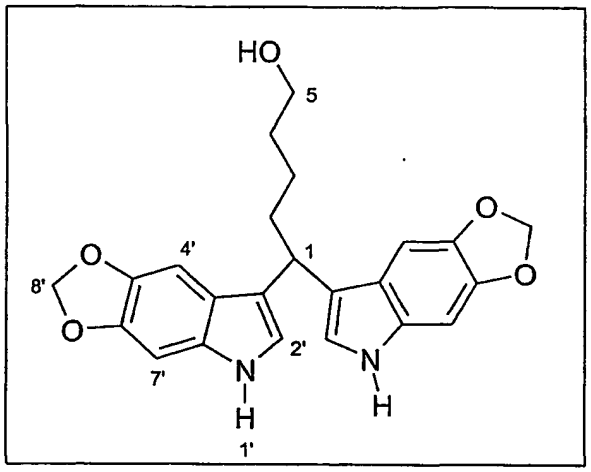
Ion Spray (M^-): 317

Elemental analysis: C:79.21% H:6.96% N:8.79% found C:78.70% H:7.29% N:8.39%.

Melting point: 190°C (dec)

EXAMPLE 3

ST 1422



5-hydroxy-1,1-di-(5,6-methylendioxy-indol-3-yl)-pentane

TLC (Hexane /iPrOH= 97.5/2.5): 0.55

HPLC RP-18 (50%H_2O, 50%CH_3CN, Flow 1ml/min): 6.7

NMR 300MHz (H-1, CD_3CN): H_1(4.2 t, 1H) - H_2(2.2 m, 2H) - H_3-H_4 (1.4-1.5 m, 2H) - H_5(3.4 q, 2H) – $H_{8'}$(5.8 s, 4H) - $H_{4'}$-$H_{7'}$ (6.8 s, 4H) - $H_{2'}$ (7.0 s, 2H) – $H_{1'}$ (8.9, brs, 2H)

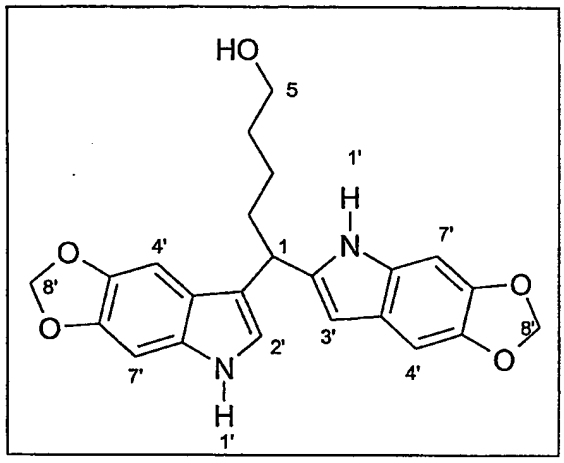
Ion Spray (M^+): 407

Elemental analysis: C:67.97% H:5.46% N:6.89% found in accordance with the theoretical.

Melting point: 200°C (dec.)

EXAMPLE 4

ST 1423



(R,S)-5-hydroxy-1,1-di-(5',6'-methylendioxy-indol-2-yl,5'',6''-methylendioxy-indol-3-yl)-pentane

TLC (Hexane/iPrOH= 97.5/2.5): 0.63

HPLC RP-18 (50%H_2O, 50%CH_3CN, Flow 1ml/min): 8.2

NMR 300MHz (H-1, CD_3CN): H_1(4.3 t, 1H) - H_2(2.2 m, 2H) - H_3-H_4 (1.4-1.6 m, 4H) - H_5(3.5 m, 2H) – $H_{8'a\text{-}8'b}$ (5.9 s, 4H) - $H_{3'b}$(6.3 s, 1H) - $H_{4'a}$-$H_{7'a}$ (6.8-6.9 d, 2H) - $H_{4'b}$-$H_{7'b}$ (7.0 d, 2H) - $H_{2'a}$(7.2 s, 1H) – $H_{1'a\text{-}1'b}$(8.9-9.1 brs-brs, 2H).

NMR 300MHz (C-13, CD_3CN): 25.1 – 33.4 – 34.9 –37.2 – 62.5 – 92.6 – 93.0 – 98.4 – 99.2 –99.7 – 101.3 – 101.5 – 121.7

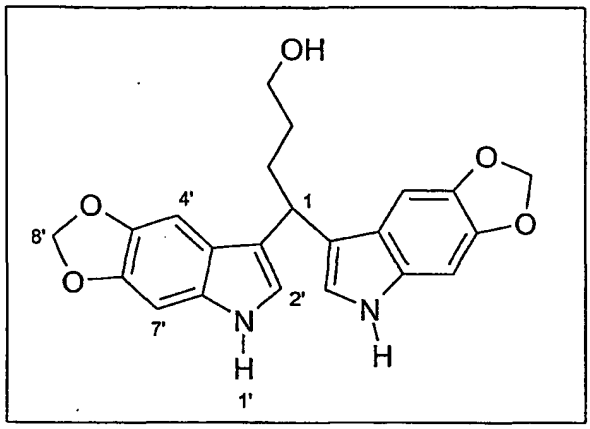
Ion Spray (M^+): 407

Elemental analysis: (calculated) C:67.97% H:5.46% N:6.89% (found) in accordance with the theoretical.

Melting point: 220°C (dec.)

EXAMPLE 5

ST1730



4-hydroxy-1,1-di-(5',6'-methylendioxy-indol-3-yl)-butane

TLC (Hexane/iPrOH= 75/25): 0.44

HPLC RP-18 (60%H_2O, 40%CH_3CN, Flow 1ml/min): 17.5

NMR 300MHz (H-1, CD_3CN): H_1(4.3 t, 1H) - H_2(2.3 m, 2H) - H_3(1.6 m, 2H) - H_4(3.6 q, 2H) – $H_{8'}$(6.0 s, 4H) - $H_{4'}$-$H_{7'}$ (6.9 s, 4H) - $H_{2'}$ (7.2 s, 2H) – $H_{1'}$ (9.0 brs, 2H)

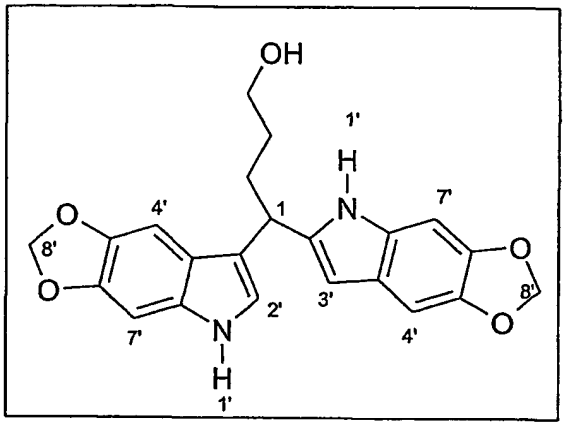
Ion Spray (M^+): 393

Elemental analysis: C:67.34% H:5.14% N:7.14% (found): in accordance with the theoretical.

Melting point: 240°C (dec.)

EXAMPLE 6

ST1731



(R,S)-4-hydroxy-1,1-di-(5',6'-methylendioxy-indol-2-yl,5'',6''-methylendioxy-indol-3-yl)-butane

TLC (Hexane/iPrOH= 75/25): 0.41

HPLC RP-18 (60%H_2O, 40%CH_3CN, Flow 1ml/min): 23.4

NMR 300MHz (H-1, CD_3CN): H_1(4.3 t, 1H) - H_2(2.2 m, 2H) - H_3(1.6 m, 4H) - H_4(3.7 m, 2H) – $H_{8'a-8'b}$ (6.0 s, 4H) - $H_{3'b}$(6.4 s, 1H) - $H_{4'a}$-$H_{7'a}$ (6.8-6.9 d, 2H) - $H_{4'b}$-$H_{7'b}$ (7.0 d, 2H) - $H_{2'a}$(7.2 s, 1H) – $H_{1'a-1'b}$(8.9-9.1 brs-brs, 2H)

NMR 300MHz (C-13, CD_3CN): 29.8 – 30.4 – 35.5 –60.8 – 90.9 – 91.4 – 96.7 – 97.5 – 98.1 –99.6 - 99.9 - 116.6 - 116.9 - 119.9 - 121.6 - 130.0 - 130.9 -141.3 -141.5 - 141.6 -142.9 - 143.8

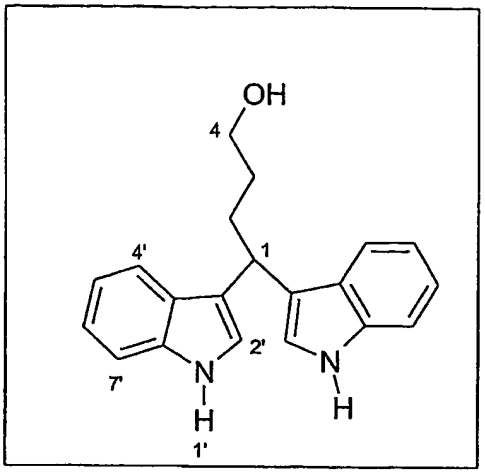
Ion Spray (M^-): 391

Elemental analysis: (calculated): C67.34% H5.14% N7.14% (found): in accordance with the theoretical.

Melting point: 205°C (dec.)

EXAMPLE 7

ST 1707



1,1-di(indol-3-yl)-4-hydroxy-butane

TLC (Hexane/AcOEt = 1/1): 0.26

HPLC RP-18 (50% H_2O, 50% CH_3CN, Flow 1ml/min): 8.3

NMR 300MHz (H-1, CD_3CN): H_1(4.3 t, 1H) - H_2(2.2 m, 2H) - H_3(1.4 m, 2H) - H_4(3.4 t, 2H) – $H_{2'}$(7.2 s, 2H) – $H_{5'}$(6.8 t, 2H) - $H_{6'}$(6.9 t, 2H) - $H_{4'}$(7.2 d, 2H) -$H_{7'}$(7.5 d, 2H) – $H_{1'}$(10.7 br.s, 2H)

NMR 300MHz (C-13, CD_3CN): C_1(61.5) - $C_{2\text{-}3}$(32.2) - C_4(34) – $C_{7'}$(112) – $C_{6'}$(118.5) - $C_{3'}$-$C_{4'}$(119.5-119.7) – $C_{5'}$(121.2) – $C_{2'}$(121.6) – $C_{3'bis}$(127.4) – $C_{7'bis}$(137.1)

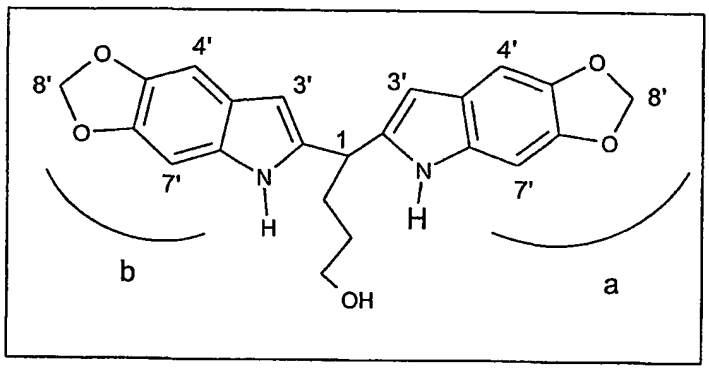
Ion Spray (M^-): 303

Elemental analysis: (calculated) C:78.92% H:6.62% N:9.20% (found) in accordance with the theoretical.

Melting point:110-115°C

EXAMPLE 8

ST 1750



4-hydroxy-1,1-di-(5',6'-methylendioxy-indol-2-yl)-butane

TLC (Hexane/iPrOH= 75/25): 0.60

HPLC RP-18 (60%H_2O, 40%CH_3CN, Flow 1ml/min): 19.9

NMR 300MHz (H-1, CD_3CN): H_1(4.3 t, 1H) - H_2(2.3 m, 2H) - H_3(1.6 m, 2H) - H_4(3.6 q, 2H) – $H_{8'}$(6.0 s, 4H) - $H_{4'}$-$H_{7'}$ (6.9 - 7.0 2s, 4H) - $H_{3'}$ (6.4 s, 2H) – $H_{1'}$ (9.1 brs, 2H)

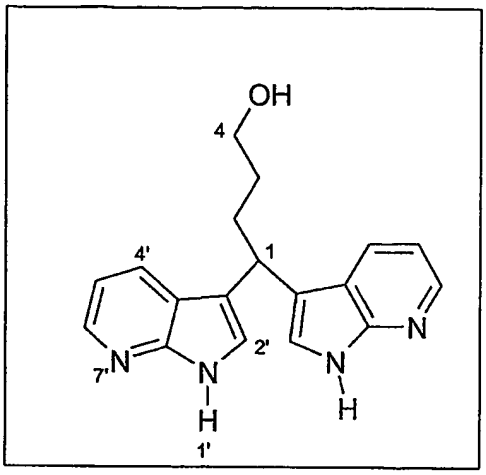
Ion Spray (M^-): 391

Elemental analysis: C:67.34% H:5.14% N:7.14% (found): in accordance with the theoretical.

Melting point: 250°C (dec.)

EXAMPLE 9

ST 1866



1,1-di(7'-aza-indol-3-yl)-4-butanol

TLC (Hexane/AcOEt = 75/25): 0.18

HPLC RP-18 (60%H_2O, 40%CH_3CN, Flow 1ml/min): 4.4

NMR 300MHz (H-1, CD_3OD): H_1(4.4 t, 1H) - H_2(2.3 m, 2H) - H_3(1.6 m, 2H) - H_4(3.6 t, 2H) – $H_{2'}$(7.3 s, 2H) – $H_{5'}$(6.9 m, 2H) - $H_{4'}$(8.1 t, 2H) - $H_{6'}$(7.8 d, 2H)

NMR 300MHz (C-13, CD_3CN): 30.3 -30.7 - 33.6 - 61.0 - 114.0 - 117.2 -119.4 - 121.9 - 127.5 -140.9 -147.7

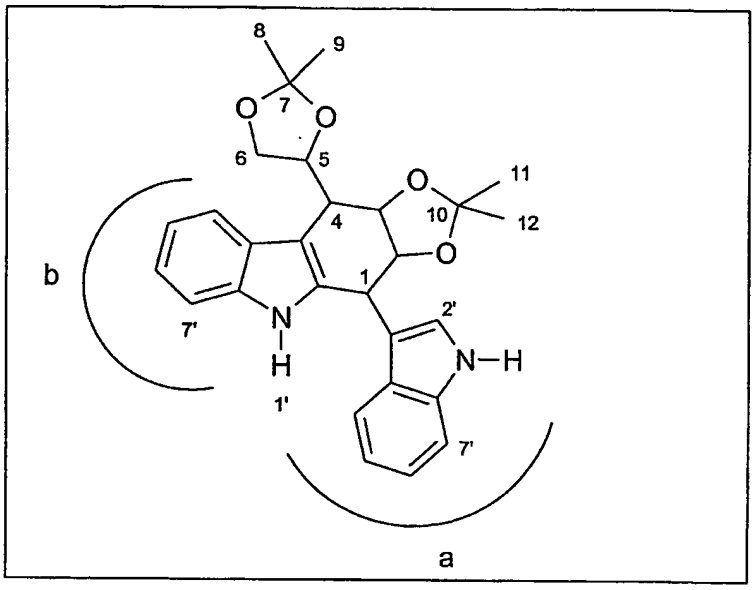
Ion Spray (M^-): 305

Elemental analysis: (calculated) C:70.57% H:5.92% N:18.29% (found) in accordance with the theoretical.

Melting point: 221°C (dec.)

EXAMPLE 10

ST 1372



1-(indol-3-yl)-2,3-O-isopropylidene-4-(2,3-O-isopropylidene-ethyl)-tetrahydrocarbazole

TLC (Hexane/Acetone=8/2): 0.75

HPLC RP-18 Waters 300x3,3(40%H_2O, 60%CH_3CN, Flow 1ml/min): 12.8

Racemic mixture

NMR 300MHz (H-1, CH_3CN): H_1+ H_3 (4.52 m, 2H) - H_2(4.64 m, 1H) - H_4(3.66 m, 1H) - H_5(4.67 m, 1H) - H_6(3.97 / 3.69 m, 2H) - H_8(1.42 s, 3H) - H_9(1.32 s, 3H) - H_{11}(1.46 s, 3H) - H_{12}(1.38 s, 3H) - $H_{2'a}$(6.94 s, 1H) - $H_{4'a}$(7.51 d, 1H) - $H_{4'b}$(7.69 d, 1H) - $H_{6'a}$ (7.16 m, 1H)

- $H_{6'b}$(7.09 m, 1H) - $H_{7'a}$(7.47 d, 1H) - $H_{7'b}$(7.26 d, 1H) - $H_{1'a}$(9.0 s, 1H) - $H_{1'b}$(8.3 s, 1H)

NMR 300MHz (C-13, CH_3CN): C_1(38.15), C_2(80.77), C_3(75.9), C_4(40.77), C_5(78.0), C_6(68.33), C_8(25.5), C_9(26.8), C_{11}(25.9), C_{12}(28.3), $C_{2'a}$(124.5), $C_{2'b}$(135.7), $C_{3'a}$(115.9), $C_{3'b}$(107.6), $C_{6'a}$(122.7), $C_{6'b}$(121.9), $C_{7'a}$(112.5), $C_{7'b}$(111.9), $C_{8'a}$(127.5), $C_{8'b}$(128.2), $C_{9'b}$(137.7), $C_{9'a}$(137.9).

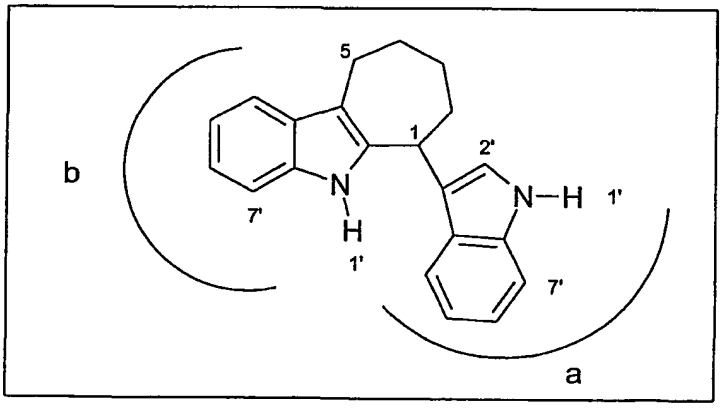
Ion Spray (M^+) 459

Elemental analysis: (calculated) C:73.34%, H:6.59%, N:6.11% (found) C:73.11%, H:6.63%, N:5.55%.

Melting point: 204-206°C (dec.)

EXAMPLE 11

ST 1381



1-(indol-3-yl)-indo[2,3a]-cycloheptan.

TLC (Hexan/iPrOH=95/5): 0.22

HPLC RP-18 Waters 300x3,3 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 22.1

Racemic mixture

NMR 300MHz (H-1, DMSO-d6): H_1(4.65 br.s,1H) - H_2(1.95 e 2.4 mm, 2H) - H_3(1.7 m, 2H) - H_4(1.6 e 1,9 mm, 2H) - H_5(2.75 e 3.0 mm, 2H) - $H_{2'a}$(6.68 s, 1H) - $H_{5'a}$ - $H_{5'b}$(6.95 m, 2H) - $H_{6'a}$(7.07 t, 1H) - $H_{4'b}$(7.45 m, 1H) - $H_{7'b}$(7.2 m, 1H) - $H_{7'a}$(7.37 d, 1H) - $H_{4'a}$(7.52 d, 1H) - $H_{1'a}$(10.8 s,1H) - $H_{1'b}$(10.4 s, 1H).

NMR 300MHz (C-13, DMSO-d6): C_1(36.3), C_2(33.2), C_3(26.5), C_4(28.6), C_5(24.0), $C_{7'b}$(110.5), $C_{7'a}$(111.4), $C_{3'a}$(115.6), $C_{4'b}$(117.2), $C_{5'b}$(117.7), $C_{5'a}$(118.2), $C_{4'a}$(118.5), $C_{6'b}$(119.7), $C_{6'a}$(120.7), $C_{2'a}$(123.5), $C_{8'a}$(125.9), $C_{8'b}$(128.6), $C_{9'b}$(134.2), $C_{9'a}$(136.6), $C_{2'b}$(139.7).

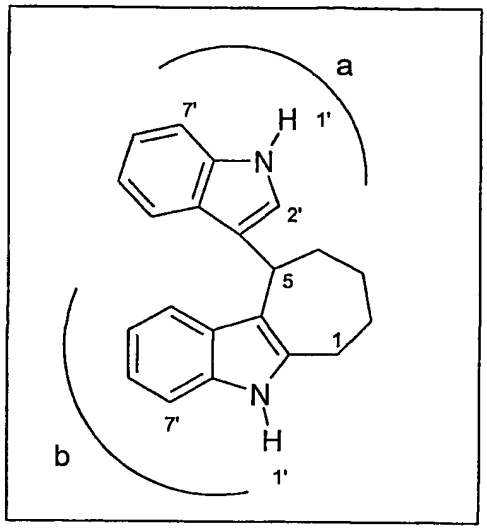
Ion Spray (M^-): 299

Elemental analysis: (calculated) C:83.96% H:6.71% N:9.33% (found) C:81.19% H:6.50% N:9.03%

Melting point: 206-208°C

EXAMPLE 12

ST 1621



5-(indol-3-yl)-indo[2,3a]-cycloheptan.

TLC (Hexan/iPrOH=95/5): 0.15

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 16.6

Racemic mixture

NMR 300MHz (H-1, DMSO-d6): H_5(4.8 br.s,1H) - H_4(1.9 and 2.4 mm, 2H) - H_3(1.5 and 1.7 mm, 2H) - H_2(1.5 and 1.9 mm, 2H) - H_1(2.9 br.s, 2H) - $H_{2'a}$(6.5 s, 1H) - $H_{5'b}$(6.8 t, 1H) - $H_{6'b}$(6.92 t, 1H) - $H_{5'a}$(6.97 t, 1H) - $H_{6'a}$(7.07 t, 1H) - $H_{4'b}$(7.13 d, 1H) - $H_{7'b}$(7.24 d, 1H) - $H_{7'a}$(7.3 d, 1H) - $H_{4'a}$(7.62 d, 1H) - $H_{1'a}$(10.6 s,1H) - $H_{1'b}$(10.7 s, 1H).

NMR 300MHz (C-13, DMSO-d6): C_3(25.2) - C_2(27.3)- C_1(28.3) - C_5(31.8) - C_4(33.7) - $C_{7'b}$(110.2) - $C_{7'a}$(111.3) - $C_{3'b}$(114.5) - $C_{4'b}$(117.1) - $C_{3'a}$(117.4) - $C_{5'b}$(117.7) - $C_{5'a}$(117.9) - $C_{4'a}$(118.6) - $C_{6'b}$(119.6) -

$C_{6'a}$(120.5) - $C_{2'a}$(123.5) - $C_{8'a}$(126.2) - $C_{8'b}$(128.5) - $C_{9'b}$(134.3) - $C_{9'a}$(136.6) - $C_{2'b}$(137.4).

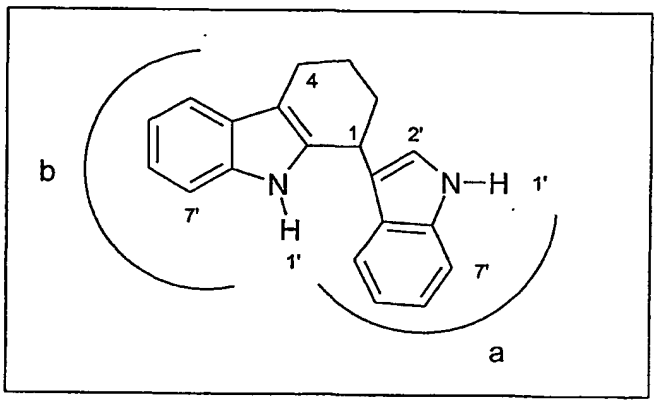
Ion Spray (M^-): 299

Elemental analysis: (calculated) C:83.96% H:6.71% N:9.33%, in accordance with the theoretical.

Melting point:170°C

EXAMPLE 13

ST 1728



1-(1H-indol-3-yl)-tetrahydro-1H-carbazole

TLC (Hexane/iPrOH=9/1): 0.66

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 18.4

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(4.46 t, 1H) - H_2(2.1 and 2.3 mm, 2H) - H_3(1.9 and 2.1 mm, 2H) - H_4(2.81 t, 2H) - $H_{2'a}$(6.98 s, 1H) - $H_{5'a}$(6.92 t, 1H) - $H_{5'b}$ - $H_{6'b}$ (7.0 m, 2H) - $H_{6'a}$(7.09 m, 1H) - $H_{7'b}$(7.15 m, 1H) - $H_{4'a}$(7.29 d, 1H) - $H_{7'a}$(7.4 dt, 1H) - $H_{4'b}$(7.46 d, 1H) - $H_{1'a}$(9.1 br.s, 1H) - $H_{1'b}$(8.6 br.s, 1H).

NMR 300MHz (C-13, , CD_3CN): C_4(21.8) – C_3(23.1) - C_2(33.0) - C_1(33.2) – $C_{3'b}$(110.6) - $C_{7'b}$(111.4) - $C_{7'a}$(112.3) - $C_{4'b}$(118.5) - $C_{3'a}$(118.7) - $C_{5'b}$(119.4) - $C_{5'a}$(119.7) - $C_{4'a}$(119.8) - $C_{6'b}$(121.5) - $C_{6'a}$(122.4) - $C_{2'a}$(123.9) - $C_{8'a}$(127.5) - $C_{8'b}$(128.6) - $C_{9'b}$(137.0) - $C_{9'a}$(137.8) - $C_{2'b}$(137.9).

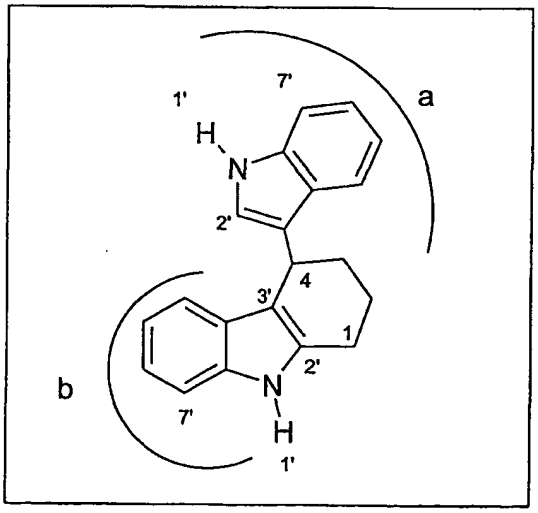
Ion Spray (M^+): 287

Elemental analysis: (calculated) C:83.30% H:6.99% N:9.71%, in accordance with the theoretical.

Melting point: 207°C

EXAMPLE 14

ST 1729



4-(1H-indol-3-yl)-tetrahydro-1H-carbazole

TLC (Hexane/iPrOH=9/1): 0.55

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow1ml/min): 12.4

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(2.83 m, 1H) - H_2(1.95 and 1.84 mm, 2H) - H_3(2.17 and 2.04 mm, 2H) - H_4(4.49 t, 1H) - $H_{2'a}$(6.77 d, 1H) – $H_{4'a}$(7.43 d, 1H) - $H_{6'a}$(7.06 t, 1H) - $H_{7'a}$(7.36 d, 1H) - $H_{5'a}$ (6.92 m, 1H) - $H_{7'b}$(7.27 d, 1H) - $H_{4'b}$(6.83 d, 1H) - $H_{5'a}$ (6.71 t, 1H) - $H_{6'b}$(6.94 m, 1H)– $H_{1'a}$(8.96 br, 1H) - $H_{1'b}$(8.94 br, 1H).

NMR 300MHz (C-13, CD_3CN): C_2(22.0) - C_1(24.0) - C_4(31.0)– C_3(33.0) - $C_{7'b}$(111.3) - $C_{7'a}$(112.3) – $C_{3'b}$(112.5) - $C_{4'a}$(119.3) - $C_{3'a}$(120.9) - $C_{6'b}$(121.2)- $C_{6'a}$(122.1) - $C_{2'a}$(123.7) - $C_{8'a}$(127.7) - $C_{8'b}$(128.5) - $C_{2'b}$(136.2) - $C_{9'b}$(137.0) - $C_{9'a}$(137.8).

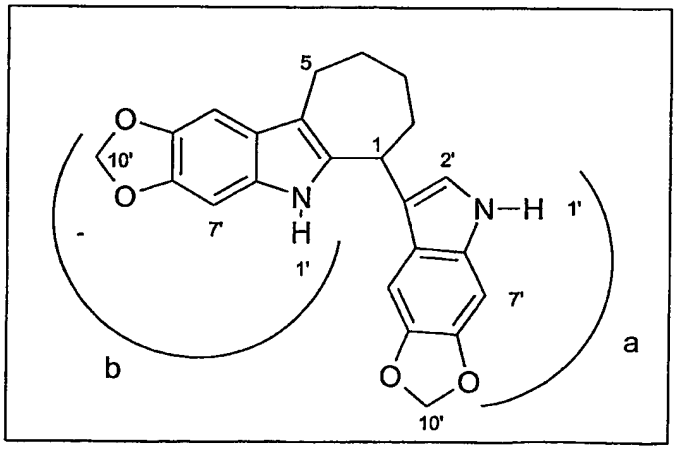
Ion Spray (M^+): 287

Elemental analysis: (calculated) C:83.30% H:6.99% N:9.71%

Melting point: 182°C

EXAMPLE 15

ST 1749



1-(5",6"-methylendioxy-indol-3-yl)-5',6'-methylendioxy-indo[2,3-a]-cycloeptane

TLC (Hexane/AcOEt = 8/2): 0.23

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 15.4

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(4.45 m, 1H) - H_2(2.05 and 2.25 mm, 2H) - H_3-H_4 (1.8 m, 4H) - H_5(2.85 m, 2H) - $H_{10'b}$(5.85 d, 1H) - $H_{10'a}$ (5.90 s, 2H) - $H_{7'b}$(6.66 s, 1H) - $H_{2'a}$(6.8 d, 1H) - $H_{4'b}$(8.3 s, 1H) - $H_{4'a}$(6.9 s, 1H) - $H_{7'a}$(6.94 s, 1H) - $H_{1'b}$(8.4 s, 1H) - $H_{1'a}$(9.0 s,1H).

NMR 300MHz (C-13, CD_3CN): C_5(25.4), C_3-C_4(29.5), C_2(35.3), C_1(38.1), $C_{7'b}$(92.4), $C_{7'a}$(93.0), $C_{4'a}$(97.3), $C_{4'b}$(98.4), $C_{10'b}$(101.1), $C_{10'a}$(101.5), $C_{3'b}$(113.4), $C_{3'a}$(118.2), $C_{8'a}$(121.3), $C_{2'a}$(121.7), $C_{8'b}$(124.0), $C_{9'b}$(129.8), $C_{9'a}$(132.7), $C_{2'b}$(139.3), $C_{6'b}$(142.9), $C_{6'a}$(143.3), $C_{5'b}$(144.3), $C_{5'a}$(145.5).

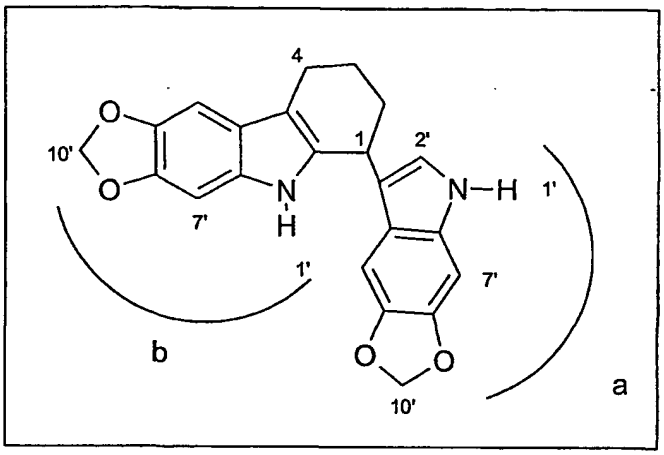
Ion Spray (M^+):389

Elemental analysis: (calculated) C:71.12% H:5.19% N:7.21% (found) in accordance with the theoretical.

Melting point: 184°C (dec.)

EXAMPLE 16

ST 1751



1-(5',6'-methylendioxy-1H-indol-3-yl)-6,7-methylendioxy-tetrahydro-1H-carbazole

TLC (Hexane/iPrOH=9/1): 0,31

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 11.5

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(4.32 t, 1H) - H_2(2.2 and 2.0 mm, 2H) - H_3(2.03 and 1.83 mm, 2H) - H_4(4.3 t, 2H) – $H_{10'a}$-$H_{10'b}$(5.8-5.9 dd, 4H) - $H_{4'a}$(6.65 s, 1H) - $H_{7'b}$(6.72 s, 1H) - $H_{2'a}$(6.88 d, 1H) - $H_{7'a}$- $H_{4'b}$(6.90 s, 1H) – $H_{1'b}$(8.4 s, 1H) - $H_{1'a}$(9.0 s, 1H).

NMR 300MHz (C-13, CD_3CN): C_4(21.8) – C_3(23.2) - C_2(33.0) - C_1(33.3) – $C_{7'b}$(92.8) - $C_{7'a}$(93.0) - $C_{4'b}$(97.6) - $C_{4'a}$(98.2)- $C_{10'a}$(101.2) – $C_{10'b}$(101.5) - $C_{3'b}$(110.8) - $C_{3'a}$(119.1) - $C_{8'a}$(121.4) - $C_{2'a}$-$C_{8'b}$(122.4) - $C_{9'b}$(131.6) - $C_{9'a}$(132.6) - $C_{2'b}$(136.6) – $C_{6'b}$(142.9) – $C_{6'a}$(143.2) – $C_{5'b}$(144.6) – $C_{5'a}$(145.4).

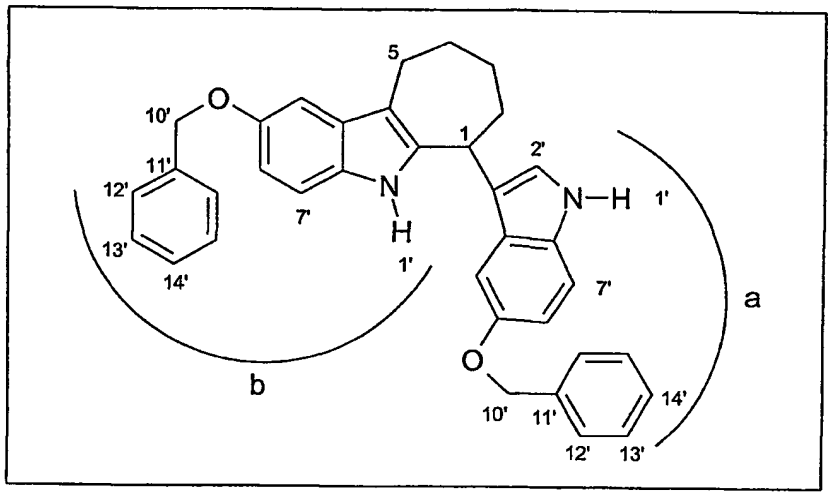
Ion Spray (M^+): 375

Elemental analysis: (calculated) C:70.58% H:4.85% N:7.48%, in accordance with the theoretical.

Melting point: 200°C (dec.)

EXAMPLE 17

ST 1765



1-(5''-benzyloxy-indol-3-yl)-5'-benzyloxy-indo[2,3a]-cycloheptan.

TLC (Hexan/iPrOH = 9/1): 0.62

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 27.1

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(4.54 d, 1H) - H_2(2.32 and 2.08 mm, 2H) - H_3(1.83 m, 2H) - H_4(1.83 m, 2H) - H_5(2.88 m, 2H) – $H_{10'a}$(4.99 s, 2H) - $H_{10'b}$(5.13 s, 2H) - $H_{5'a}$ - $H_{5'b}$(6.95 m, 2H) - $H_{6'b}$(6.74 q, 1H) - $H_{6'a}$(6.87 q, 1H) – $H_{2'a}$(6.90 d, 1H) - $H_{4'a}$(6.93 d, 1H) - $H_{7'b}$(7.07 d, 1H) - $H_{4'b}$(7.09 d, 1H) – $H_{14'a}$ - $H_{14'b}$ (7.31-7.27 m, 2H) -

$H_{7'a}$(7.34 m, 1H) - $H_{13'a}$(7.33 m, 1H) - $H_{13'b}$(7.38 m, 1H) - $H_{12'a}$(7.39 d, 1H) - $H_{12'b}$(7.47 d, 1H) - $H_{1'b}$(8.47 s,1H) - $H_{1'a}$(9.0 s, 1H).

NMR 300MHz (C-13, CD_3CN): C_1(38.01), C_2(35.1), C_3(29.5), C_4(29.4), C_5(25.3), $C_{10'a}$ (71.3) $C_{10'b}$(71.4), $C_{4'b}$(102.5), $C_{4'a}$(103.7), $C_{6'b}$(111.7), $C_{7'b}$(112.0), $C_{7'a}$(113.1), $C_{3'b}$–$C_{6'a}$ (113.2), $C_{3'a}$(117.4), $C_{2'a}$(125.0), $C_{8'a}$(127.9), $C_{12'b}$(128.5), $C_{12'a}$(128.6), $C_{13'a}$(129.3), $C_{13'b}$(129.4), $C_{8'b}$(130.5), $C_{9'b}$(130.7), $C_{9'a}$(133.2), $C_{11'a}$(139.0), $C_{11'b}$(139.3), $C_{2'b}$(141.7), $C_{7'a}$(113.0), $C_{6'a}$–$C_{3'a}$ (113.2), $C_{14'a}$–$C_{14'b}$-$C_{12'b}$ (128.5), $C_{12'a}$(128.6)

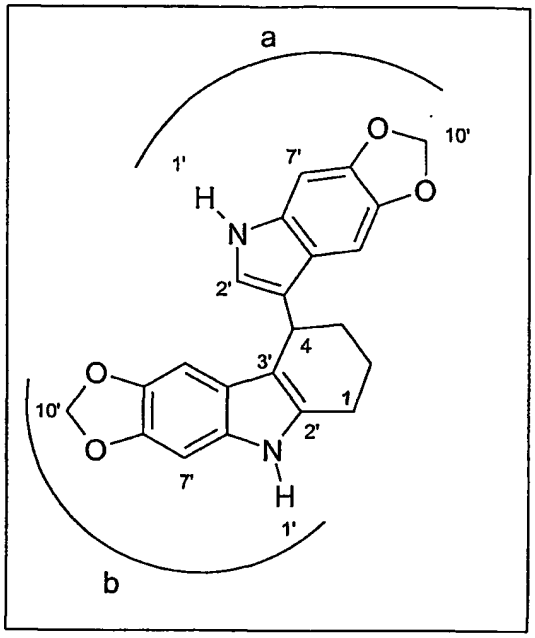
Ion Spray (M^+): 513

Elemental analysis: (calculated) C:82.00% H:6.29% N:5.46% - (found) in accordance with the theoretical.

Melting point: 286°C (dec.)

EXAMPLE 18

ST 1777



4-(5',6'-methylendioxy-1H-indol-3-yl)-6,7-methylendioxy-tetrahydro-1H-carbazole

TLC (Hexane/iPrOH=9/1): 0.20

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 7.9

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(2.80, 1H) - H_2(1.96 and 1.84 mm, 2H) - H_3(2.13 and 1. mm, 2H) - H_4(4.31 t, 1H) – $H_{10'b}$(5.76 d, 2H) – $H_{10'a}$(5.,86 d, 2H) - $H_{4'b}$(6.22 s, 1H) - $H_{4'a}$(6.74 s, 1H) - $H_{2'a}$(6.75 d, 1H) – $H_{7'b}$(6.82 s, 1H) - $H_{7'a}$(6.88 s, 1H) - $H_{1'b}$(8.83 s, 1H) - $H_{1'a}$(8.86 s, 1H).

NMR 300MHz (C-13, CD_3CN): C_2(22.3) - C_1(23.9) - C_4(31.7) – C_3(33.1) - $C_{7'b}$(92.7)- $C_{7'a}$(93.0) – $C_{4'b}$(98.3) - $C_{4'a}$(98.5) – $C_{10'b}$(101.1) – $C_{10'a}$(101.4) – $C_{3'b}$(112.8) – $C_{3'a}$(120.9) - $C_{8'a}$(121.5) - $C_{8'b}$-$C_{2'b}$ (122.,3) - $C_{9'b}$(131.6) - $C_{9'a}$(132.6) – $C_{2'b}$(134.7) – $C_{6'b}$(142.4) – $C_{6'a}$(142.9) – $C_{5'b}$(144.2) - $C_{5'a}$(145.2).

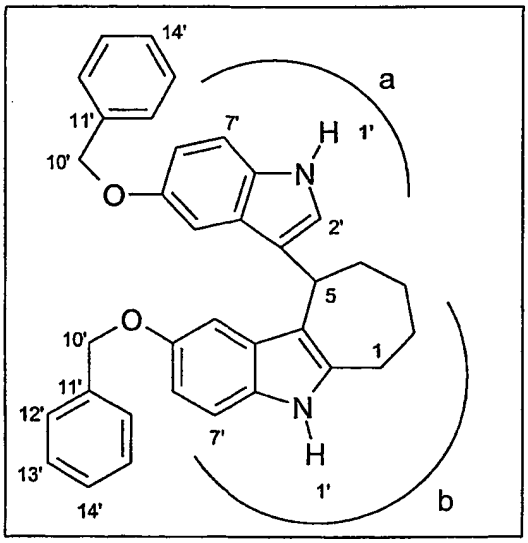
Ion Spray (M^-): 373

Elemental analysis: (Calculated) C:70.20% H:5.36% N:7.44%, in accordance with the theoretical.

Melting point: 228°C (dec.)

EXAMPLE 19

ST 1778



5-(5''-benzyloxy-indol-3-yl)-5'-benzyloxy-indo[2,3a]-cycloheptan.

TLC (Hexane/iPrOH = 9/1): 0.4

HPLC RP-18 (40%H_2O, 60%CH_3CN, Flow 1ml/min): 18.1

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(2.89 m,1H) - H_4(2.49 m, 2H) - H_3(1.6 and 1.8 mm, 2H) - H_2(1.6 m, 2H) - H_5(4.72 t, 1H) – $H_{10'b}$(4.89 d, 2H) – $H_{10'a}$(5.08 s, 2H) – $H_{2'a}$(6.54 d, 1H) - $H_{6'b}$(6.68 q, 1H) - $H_{4'b}$(6.75 d, 1H) - $H_{6'a}$(6.83 q, 1H) - $H_{7'b}$(7.16 d, 1H) - $H_{4'a}$(7.16 d, 1H) – $H_{7'a}$(7.28 d, 1H) - $H_{13'b}$(7.29 m, 1H) - $H_{12'b}$(7.34 m,1H) - $H_{13'a}$(7.37 m, 1H) - $H_{12'a}$(7.47 d, 1H) - $H_{1'a}$(8.90 s, 1H) – $H_{1'b}$(8.93 s, 1H).

NMR 300MHz (C-13, CD_3CN): C_3(26.6) - C_2(28.5) – C_1(29.7)- C_5(33.4) – C_4(34.7) - $C_{10'b}$(71.2) - $C_{10'a}$(71.4)- $C_{4'b}$(112.5) - $C_{4'a}$(104.0) - $C_{6'b}$(111.6) - $C_{6'a}$(111.8) - $C_{7'b}$(112.9) - $C_{7'a}$(112.9) - $C_{3'b}$(116.1) - $C_{3'a}$(119.2) - $C_{2'a}$(125.3) - $C_{8'a}$(128.1) – $C_{14'b}$(128.5) – $C_{14'a}$(128.6) – $C_{12'b}$(128.6) – $C_{12'a}$(128.7) – $C_{13'a}$(129.2) – $C_{13'b}$(129.3) - $C_{8'b}$(130.5) - $C_{9'b}$(131.0) – $C_{9'a}$(133.3) - $C_{11'a}$-$C_{11'b}$(139.1) - $C_{2'b}$(139.7) - $C_{5'a}$(153.3) – $C_{5'b}$(153.5).

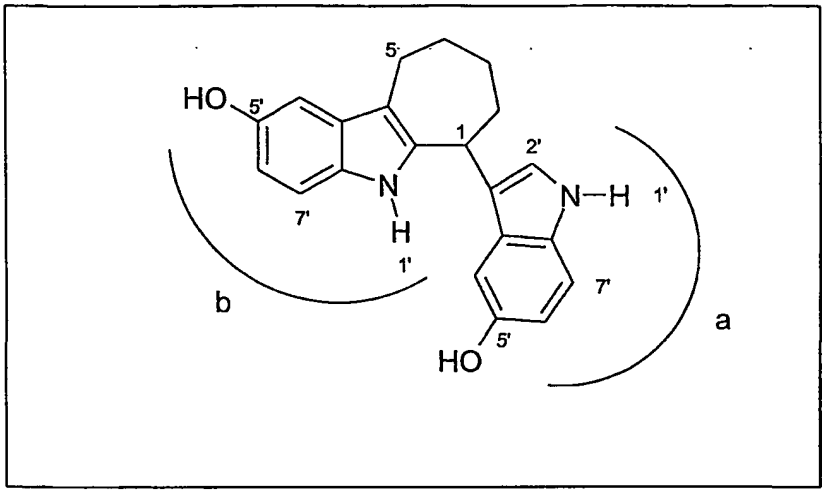
Ion Spray (M^-): 511

Elemental analysis: (calculated) C:82.00% H:6.29% N:5.46%, in accordance with the theoretical.

Melting point: 237°C (dec.)

EXAMPLE 20

ST1783



1-(5''-hydroxy-1H-indol-3-yl)-5'-hydroxy-indo[2,3a]-cycloheptan.

TLC (Hexane/iPrOH = 9/1): 0.35

HPLC RP-18 Waters 300 x 3,3 (45%H_2O, 55%CH_3CN, Flow 1ml/min): 4.2

Racemic mixture

NMR 300MHz (H-1, CD_3CN): H_1(4.61 d, 1H) - H_2(2.3 and 2.0 mm, 2H) - H_3(1.9 m, 2H) - H_4(1.8 m, 2H) - H_5(2.97 m, 2H) – OH(6.45 br.d, 2H) - $H_{7'b}$(6.67 d, 1H) - $H_{7'a}$(6.83 d, 1H) - $H_{4'a}$ $H_{4'b}$(6.95 s, 2H) – $H_{2'a}$(7.0 s, 1H) - $H_{6'b}$(7.1 d, 1H) - $H_{6'a}$(6.4 d, 1H) – $H_{1'b}$(8.44 s,1H) - $H_{1'a}$(9.01 s, 1H).

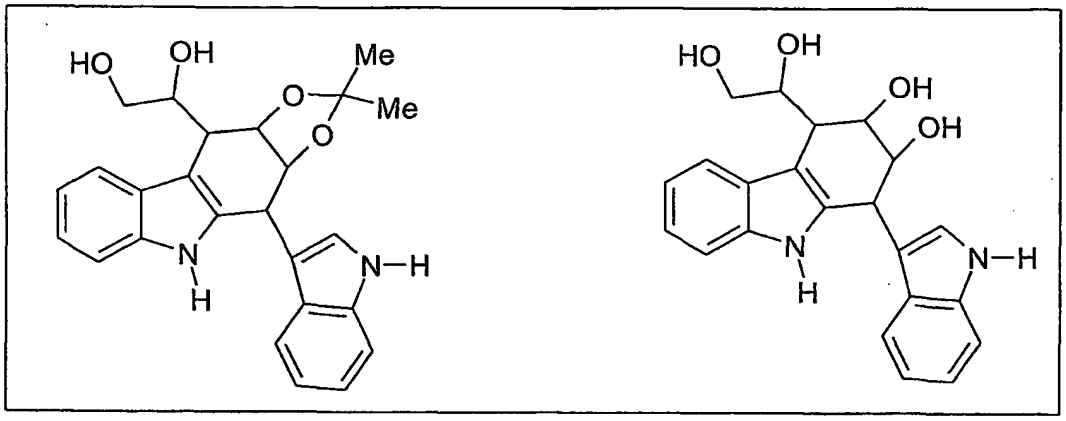
NMR 300MHz (C-13, CD_3CN): C_1(36.6), C_2(33.6), C_3(28.1), C_4(28.0), C_5(23.8), $C_{4'b}$(101.1), $C_{4'a}$(102.4), $C_{6'b}$(109.1), $C_{7'b}$(110.1), $C_{7'a}$(110.7), $C_{3'b}$–$C_{6'a}$ (111.0), $C_{3'a}$(115.3), $C_{2'a}$(126.5), $C_{8'a}$(128.4), $C_{8'b}$(128.6), $C_{9'b}$(129.2), $C_{9'a}$(131.0), $C_{2'b}$(140.1), $C_{5'a}$ - $C_{5'b}$ (149.3).

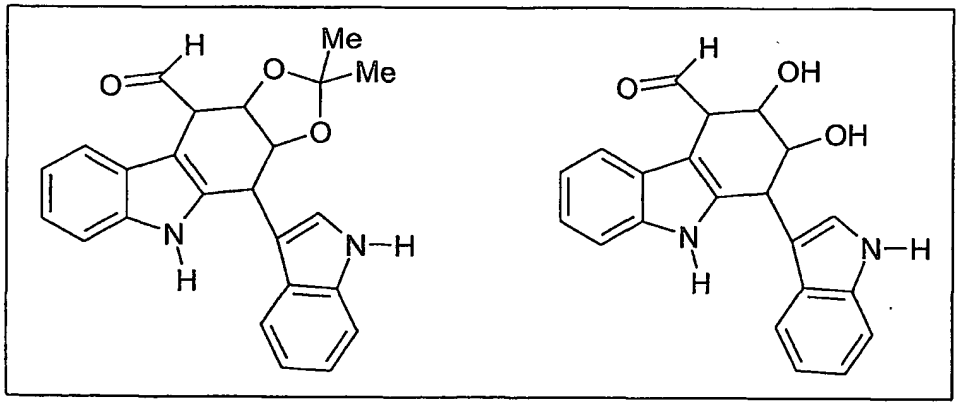
Ion Spray (M^+): 333

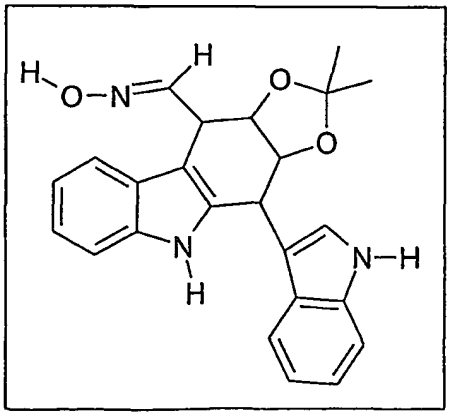
Elemental analysis: (calculated) C:75.88% H:6.06% N:8.43% (found) in accordance with the theoretical.

EXAMPLE 21

In the similar way were prepared the following compounds:







COMPOUND	PROCEDURE	NOTE
ST1866	A	Bis-7-azaindolyl *via* magnesiumbromide
ST1345	B	Bis-indolyl *via* acid catalysis
ST1346	B	"
ST1422	B	"
ST1423	B	"
ST1707	B	"
ST1750	B	"
ST1372	C	Cyclization of sugar moieties
ST1381	D	Cyclization of the non-sugar moieties
ST1621	D	"
ST1728	D	"
ST1729	D	"
ST1749	D	"
ST1751	D	"
ST1765	D	"
ST1777	D	"
ST1778	D	"
ST1783	E	Debenzylation
ST 1900	F	Deprotection
ST 1901	F	Deprotection
ST (all)	G	Oxydation

Pharmacology

The abbreviation ST, followed by a number, identifies the compounds figuring in the examples reported in the pharmacological assays.

For the antiangiogenic activity the chemotactic assay with the Boyden chamber was performed (Werner F., Goodwin R.H. and Leonard E.J., Journal of Immunological Methods 1980; 33, 239-247), using both bovine aortal endothelial cell (BAEC) cultures and bovine medullary endothelial cell (BMEC) cultures. The assays were performed at IC_0 (maximum non-cytotoxic concentration) and the results expressed as % inhibition of migration across a porous filter in response to a chemotactic stimulus (1% bovine serum in DMEM culture medium). This finding was obtained by direct cell count under the optical microscope, and the percentage migration inhibition was calculated according to the formula (T-C/C)x100, where T = mean number of cells migrating in the sample and C = mean number of cells migrating in the control. The control consisted of cells which migrated towards the serum, not treated with the study molecules, and included in every chemotaxis experiment. The data refer to the readings of 5 microscopic fields/well in 4 independent chemotaxis wells per sample. The results obtained are reported on Table 4.

For the cytotoxic activity, proliferation screening tests were used, with different tumour lines, such as MCF-7 (human mammary

carcinoma), LoVo (human colon carcinoma), MES-SA (human uterine sarcoma), or K-562 (human chronic myeloid leukaemia).

The test used was the sulforodamine B test used for screening anticancer products at the National Cancer Institute (Skehan, 1990). The molecules at scalar concentrations over a range from 500 μM to 0.97 μM, were incubated in parallel with different human cell lines for 24 hours. After removing the products, cell survival was investigated after another 48 hours with the NCI test. The antiproliferative capacity of the compounds was quantified in terms of $IC_{50} \pm SD$ (concentration of the molecule that inhibits 50% of cell survival) processed using a curve fitting program (De Lean et al., 1978). The results obtained are reported on Table 1 and Table 2.

The cell cycle and apoptosis analysis on a tumour line was done by incubating the products for 24 hours at a concentration equal to approximately the IC_{50} values with MCF-7 cells. The molecules were removed and the cell cycle and apoptosis were assessed at different times (0, 24, 48 hours). The cells were stained with propidium iodide and analysed with a cytofluorimeter (FACS) (Beckman Dickinson fluorescence activated cell sorter) by means of an argon ion laser set at 488 nm for the excitation. To assess the percentage of cells in the various stages of the cycle, linear DNA histograms were analysed with a cell fit program distributed by the equipment manufacturer. For the analysis of apoptosis, a region was inserted below the G0/G1 peak of the control population and the

data were analysed with software supplied by the company (Lysis II-C32). The results obtained are reported on Table 3.

The cytotoxicity of the molecules on tumour lines resistant to chemosensitising activity was assessed on various tumour cell lines overexpressing P-glycoprotein and resistant to doxorubicin (100-fold) and cross-resistant to daunorubicin, actinomycin D, mitoxantrone, vincristine, vinblastine, taxol, colchicine, and etoposide. The cytotoxicity of the products was assessed using the same test adopted for the sensitive tumour cells.

Later, the products were assayed at a concentration lower than or equal to the one that inhibits 10% of cell survival. At this concentration, the molecules were tested in parallel in the absence and presence of doxorubicin. MDR ratios were calculated for the IC_{50} values in order to establish the degree of potentiation of the cytotoxic activity of doxorubicin induced by the product (MDR ratio) (De Lean et al. (1978) A. J. Physiol. 235, E97-102); (Skehan et al. (1990) J. Natl. Cancer Inst. 82, 1107-1112).

TABLE 1

ANTIPROLIFERATIVE ACTIVITY vs SENSITIVE CELL

Series	Compound	IC_{50} +/- SD (μM)	
		MCF-7	LoVo
Tetrahydrocarbazoles	ST1372	21,1+/-0,3	21,7+/-4,3
"	ST1728	22+/-2,8	22,8+/-2,9
"	ST1729	35+/-6,1	50,5+/-4,8
"	ST1777	0,96+/-0,19	0,64+/-0,003
Esahydrocycloept[b]indoles	ST1381	28,5+/-1,8	22,5+/-2,6
"	ST1621	22,5+/-1,3	34,8+/-4,3
"	ST1765	11,5+/-1,1	10,5+/-0,07
"	ST1778	28,5+/-1,4	54,5+/-7,4
"	ST1783	27+/-4	29+/-0,06

TABLE 2

ANTIPROLIFERATIVE ACTIVITY vs RESISTENT CELL

Series	Compound	IC_{50} +/- SD (μM)	
		MCF-7/DX	LoVo/DX
Tetrahydrocarbazoles	ST1372	26,9+/-1,6	26,3+/-3,7
"	ST1751	58,6+/-9	
EsahydroCycloept[b]indoles	ST1381	28,4+/-3	25,2+/-4,2
"	ST1621	68,3+/-4,6	23,8+/-3,7
"	ST1765	24,8+/-3,8	17,03+/-0,91
"	ST1778	71+/-0,4	65,1+/-8,1
"	ST1783	39+/-0.03	

5

TABLE 3

CELLULAR CYCLE AND APOPTOSIS ON MCF-7 CELL

Compound	G0/G1 (%)	S(%)	G2+M (%)	Apoptosis 48h (%)
ST1372	C=43,7 40μM=57,8 20μM=54,4	C=47,6 40μM=36,8 20μM=34,2	C=8,6 40μM=5,4 20μM=11,4	C =3,3 40μM=16
ST1381	C=43,8 30μM=57,7	C=47,6 30μM=32,2	C=8,6 30μM=10,1	C=3,3 30μM=3,3

ST1372 at 40 μM increases and blocks in G0/G1 32% of the cell, and at 20 μM increases and blocks in G0/G1 23% of the cell.

ST1372 at 11 μM increases 3,5 times the activity of the Doxorubicin both on MCF-7/Dx line and on LoVo/Dx cell line.

ST1381 at 30 μM increases and blocked in G0/G1 32% of the cell line; is not cytotoxic vs endotelial cell (IC>100 μM); and is active for the chemotaxys.

TABLE 4

CYTOTOXYCITY AND CHEMOTAXYS ON BMEC

Series	Compound	MEC		
		IC_{50} (μM)	IC_0 (μM)	% inhibition of migration at IC_0/D.S.
Esahydrocycloept [b]indoles	ST1381	>100	30	-61,7+/-6,3
"	ST1621	10	0,1	-43+/-4
"	ST1749	> 200	100	-40+/-3
"	ST1778	50	25	-40+/-4
"	ST1783	60	10	-46
"	ST1729	80	25	-40+/-3

Although ST 1381 results the better anti-chemiotactic compound, is important to note that all compounds of this group decrease the chemiotaxis of endothelial cells.

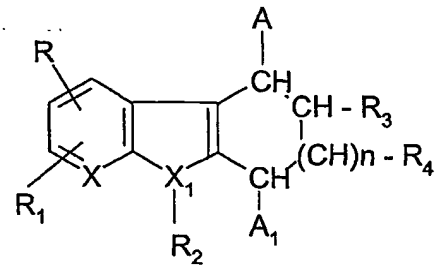
The composition according to the invention contain as active ingredient at least one formula (I) alone or in combination with other active ingredients useful in the treatment of the diseases indicated in the invention described herein, in the form of separate doses or in forms suitable for combined therapies. The active ingredient according to the invention will be in a mixture with appropriate vehicles and/or excipients commonly used in pharmacy, such as, for instance, those described in "Remington's Pharmaceutical Sciences Handbook", latest edition. The compositions according to the invention will contain a therapeutically effective amount of the active ingredient. The doses will be determined by the expert in the sector, for example the clinician or primary-care physician, according to the type of disease to be treated and the patient's condition, or concomitantly in conjunction with the administration of other active ingredients.

Examples of pharmaceutical compositions are those that allow oral or parenteral, intravenous, intramuscular, subcutaneous or transdermal administration. Pharmaceutical compositions suitable for the purpose are tablets, rigid or soft capsules, powders, solutions, suspensions, syrups, and solid forms for extempore liquid

preparations. Compositions for parenteral administration are, for example, all the intramuscular, intravenous, and subcutaneous injectable forms, in the form of solutions, suspensions or emulsions. Also worthy of mention are the liposomal formulations. Suitable compositions also include forms based on slow release of the active ingredient, whether as oral administration forms, tablets coated with suitable layers, microencapsulated powders, cyclodextrine complexes, or depot forms. e.g. subcutaneous, such as depot injections or implants.

CLAIMS

1. Compounds having formula (I):



(I)

wherein:

X = CH, N

X_1 = O, S, N, CH

R and R_1, which may be the same or different, are selected from the group consisting of: -H, OH, OR_5 in which R_5 may be C_1-C_4 alkyl or benzyl, when two groups OR_5 are vicinal R_5 is methylen; or R and R_1 may be independently nitro; amino possibly mono- or di-substituted with C_1-C_4 alkyl; carboxy; alkoxy (C_1-C_4) carbonyl;

R and R_1 taken together may form an aliphatic or aromatic cyclic group having 5 or 6 atoms;

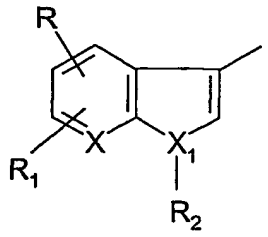
when X_1 = N, CH, then

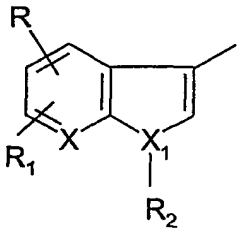
R_2 is selected from the group consisting of –H, phenyl, benzyl, linear or branched C_1-C_6 alkyl;

n = is an integer ranging from 0 and 4;

R_3, which may be the same as or different from R_4, may be: -H, -OH, - OR_6, wherein

R_6 is linear or branched C_1-C_4 alkyl, or when R_3 = R_4 = OR_6 vicinal, R_6 is isopropyliden

A =  with A_1 = H

A_1 =  with A = H, R_7

R_7 = C_1-C_4 linear or branched alkyl possibly substituted with one or two groups OH, OR_6, in case of 2 groups OR_6 vicinal, R_6 is isopropyliden; or R_7 is formyl (CHO), oxime (CH=NOH), their isomers and their mixtures, metabolites and their metabolic precursors or bio-precursors.

2. Compounds of claim 1 as medicaments.

3. Pharmaceutical composition containing as active ingredient a compound of claim 1, and at least a pharmaceutically acceptable excipient and/or diluent.

4. Composition of claim 3, for the treatment of a tumour pathology, in which the tumour is selected from the group consisting of sarcoma, carcinoma, carcinoid, bone tumour, neuroendocrine tumour, lymphoid leukaemia, acute promyelocytic leukaemia, myeloid leulaemia, monocytic leukaemia, megakaryoblastic leukaemia and Hodgkin's disease.

5. Composition of claim 3, for the treatment of pathologies caused by abnormal angiogenesis.

6. Composition of claim 5, in which the pathology caused by abnormal angiogenesis is selected from the group consisting of tumour metastases; arthritic disease; diabetic retinopathy; psoriasis; chronic inflammatory diseases or arteriosclerosis.

7. Combination consisting of a compound of formula (I) with one or more known anticancer drug, in which the known anticancer drug is selected from the group consisting of alkylating agents, topoisomerase inhibitors, antitubulin agents, intercalating compounds, anti-metabolites, natural products such as vinca alkaloids, epipodophyllotoxins, antibiotics, enzymes, taxans, cyto-differentiating compounds or anti-angiogenic compounds.

8. Pharmaceutical composition comprising as active ingredient the combination of claim 7 and one or more excipients or vehicles pharmacologically acceptable.

9. Composition of claim 8, characterised in that the compound of formula (I) is present as a co-adjuvant of the anticancer compound.

10. Composition of claim 8, characterised in that the compound of formula (I) and the known anticancer drugs are administered simultaneously or sequentially.

11. Composition of claim 3 or 8, in the form of tablets, capsules, powders, solutions, suspensions, vials, syrups, suppository, enema, foam or liposomal formulations, useful for oral, parenteral or rectal administration.

12. Use of a compound of claim 1, for the preparation of a medicament for the treatment of a tumour pathology, in which the tumour is selected from the group consisting of sarcoma, carcinoma, carcinoid, bone tumour, neuroendocrine tumour, lymphoid leukaemia, acute promyelocytic leukaemia, myeloid leukaemia, monocytic leukaemia, megakaryoblastic leukaemia and Hodgkin's disease.

13. Use of a compound of claim 1, for the preparation of a medicament for the treatment of pathologies caused by abnormal angiogenesis.

14. Use according to claim 13, in which the pathology caused by abnormal angiogenesis is selected from the group consisting of tumour metastases; arthritic disease; diabetic retinopathy; psoriasis; chronic inflammatory diseases or arteriosclerosis.

15. Use of a compound of claim 1, in combination with one or more known anticancer drug, for the preparation of a medicament with antitumor activity.

16. Use according to claim 15 in which the known anticancer drug is selected from the group consisting of alkylating agents, topoisomerase inhibitors, antitubulin agents, intercalating compounds, anti-metabolites, natural products such as vinca alkaloids, epipodophyllotoxins, antibiotics, enzymes, taxans, cyto-differentiating and anti-angiogenic compounds .

17. Use according claim 15, in which the compound of formula (I) and the known anticancer drugs are administered simultaneously or sequentially.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 01/00526

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 C07D471/04 C07D209/80 C07D209/86 A61K31/404 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 614 888 A (HOECHST ROUSSEL PHARMA) 14 September 1994 (1994-09-14) the whole document ---	1-17
A	EP 0 496 314 A (HOECHST ROUSSEL PHARMA) 29 July 1992 (1992-07-29) the whole document -----	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2002	26/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Johnson, C

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (part)

In claim 1 compounds of formula (I), their metabolites and their metabolic precursors or bio-precursors are claimed. The metabolites and precursors are not defined in any more precise way in the remaining claims or description. In order to identify possible compounds falling within these definitions, the reader would have to perform extensive in vivo tests, and even then the scope of the claim would not be unambiguously clear, as no conditions are given under which the metabolites should be formed. In view of the lack of clarity (Article 84 EPC) and the lack of disclosure (Article 83 EPC), the search has been limited to the scope of claim 1 that is clear, i.e. to the compounds of formula (I) as defined in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ternational Application No
PCT/IT 01/00526

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0614888 A	14-09-1994	US 5350762 A	27-09-1994
		AT 152709 T	15-05-1997
		CA 2117164 A1	09-09-1994
		DE 69403015 D1	12-06-1997
		DE 69403015 T2	09-10-1997
		DK 614888 T3	03-11-1997
		EP 0614888 A1	14-09-1994
		ES 2101373 T3	01-07-1997
		GR 3024187 T3	31-10-1997
		JP 2749259 B2	13-05-1998
		JP 6321898 A	22-11-1994
EP 0496314 A	29-07-1992	US 5100891 A	31-03-1992
		AT 158790 T	15-10-1997
		AU 650315 B2	16-06-1994
		AU 1027992 A	23-07-1992
		BR 9200171 A	06-10-1992
		CA 2059610 A1	19-07-1992
		CS 9200129 A3	12-08-1992
		DE 69222444 D1	06-11-1997
		DE 69222444 T2	04-06-1998
		DK 496314 T3	18-05-1998
		EP 0496314 A1	29-07-1992
		ES 2109953 T3	01-02-1998
		FI 920192 A	19-07-1992
		FI 970396 A	30-01-1997
		FI 970397 A	30-01-1997
		FI 20001775 A	10-08-2000
		GR 3025318 T3	27-02-1998
		HU 67027 A2	30-01-1995
		IE 920149 A1	29-07-1992
		JP 2665422 B2	22-10-1997
		JP 4334367 A	20-11-1992
		KR 230881 B1	15-11-1999
		MX 9200206 A1	01-08-1992
		NO 178397 B	11-12-1995
		NZ 241305 A	26-10-1994
		PL 169417 B1	31-07-1996
		PL 167465 B1	30-09-1995
		RO 112505 B1	30-10-1997
		RU 2077530 C1	20-04-1997
		US 5472975 A	05-12-1995
		US 5514700 A	07-05-1996
		US 5192789 A	09-03-1993
		US 5298626 A	29-03-1994
		ZA 9200341 A	30-09-1992